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Contribution of bacterial-fungal balance to plant and animal health

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Surfaces of plants and animals are colonized by complex multi-kingdom microbial communities that comprise prokaryotic (i.e. archaea, bacteria) and eukaryotic (i.e. fungi, protists) microbes. Composition and variation in these multi-kingdom microbial communities are influenced by host and environmental cues that drive microbial community differentiation between host niches. Recent evidence indicates that, beyond these major forces, interactions between microbiota members also contribute to the establishment, the stability, and the resilience of host-associated microbial communities. Particularly, the interplay between bacteria and fungi in host niches appears critical for community functionality and alteration of the balance between these microbes emerges as a potential cause of disease. Here, we discuss the extent to which interactions between these microbes drive variation in community composition across plant and animal niches and we provide examples illustrating that altering bacterial-fungal balance in the microbiome can lead to disease.

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Introduction

Plants and animals engage in intimate association with a diversity of microbes that evolved in different kingdoms of life such as archaea, bacteria, fungi, and protists. Given the fact that most examples illustrating the relevance of microbial cross-kingdom interactions for host health derive from interactions between bacteria and fungi, we have focused our discussion on these two microbial groups. These mixed bacterial-fungal communities colonize internal and external surfaces of plant and animal host and although intracellular microbial colonisation is uncommon in animals, plant tissues are frequently colonised by both bacteria and filamentous eukaryotes [1].

In plants and animals, the bacterial fraction of host-associated multi-kingdom microbial assemblages has received extensive attention, consistent with the fact that bacterial reads represent >94% and >99% of the microbial sequences detected in plant rhizosphere and human stool metagenome samples, respectively [2–6]. However, metatranscriptomic analyses revealed that the proportion of fungal reads could account for up to 15% of the total read counts in rhizosphere samples of pea and oat [7]. Generally, bacterial community composition, variation, and functions that include enhanced nutrition, immunomodulation, or pathogen protection have been reported across plant and animal kingdoms [8]. Similarly, the diversity and beneficial activities of host-associated fungi also emerge as important forces driving microbial community stability and host health status [9–14]. Notable examples of beneficial fungi include mycorrhizal fungi that engage in symbiotic associations with roots of most land plants, likely shaping the distribution of plant species worldwide [15], as well as probiotic yeasts such as *Saccharomyces boulardii* in humans that have been prescribed since decades for prophylaxis and treatment of diarrheal diseases [16]. In the animal gut, both bacterial and fungal commensals can prevent local tissue injury, trigger systemic immune modulation [9] and contribute to host digestion and nutrient acquisition [17]. Similarly, plant roots host complex microbial communities in which both fungal and bacterial commensals have been shown to provide protection against microbial pathogens, modulate host immune outputs, and improve nutrient acquisition [18,19]. Notably, bacterial-fungal co-inoculation often results in improved plant survival, growth or productivity compared to single inoculations, illustrating that functional complementarity between bacteria and fungi is likely influencing important ecosystem functions [10,20••]. Thus, selective pressures acting on both the host and the microbiota have likely favoured the co-existence and the maintenance of multi-kingdom microbial consortia in plant and animal niches.

Dysbiosis, defined as an imbalanced microbiota has often been associated with disease in plants and animals but, in most cases, it remains unclear whether microbial dysbiosis is the cause or the consequence of a particular disease [21–23]. Few studies have experimentally demonstrated a direct causal relationship between microbial imbalance and disease using microbiota reconstitution

and transplant experiments with germ-free mice or germ-free plants [20••,24]. Particularly, manipulation of the balance between bacteria and fungi in host-associated microbiomes using antibiotic treatments, microbial transplants, or experiments with synthetic microbial communities suggest a direct connection between bacterial-fungal dysbiosis and particular diseases [20••,25,26,27•].

Bacterial-fungal interactions have been discussed in the context of ecosystem functioning or host fitness [see Refs. 28–30] but community-level understanding of how these complex interactions affect host health and disease is largely lacking. In this article, we discuss composition and variation of host-associated bacterial and fungal communities across plant and animal niches, connectedness between bacterial and fungal taxa in the microbiome, and link between bacterial-fungal imbalance and host disease. By examining commonalities between bacterial-fungal interactions across plants and animals niches, we suggest that maintenance of bacterial-fungal homeostasis is key for plant and animal health.

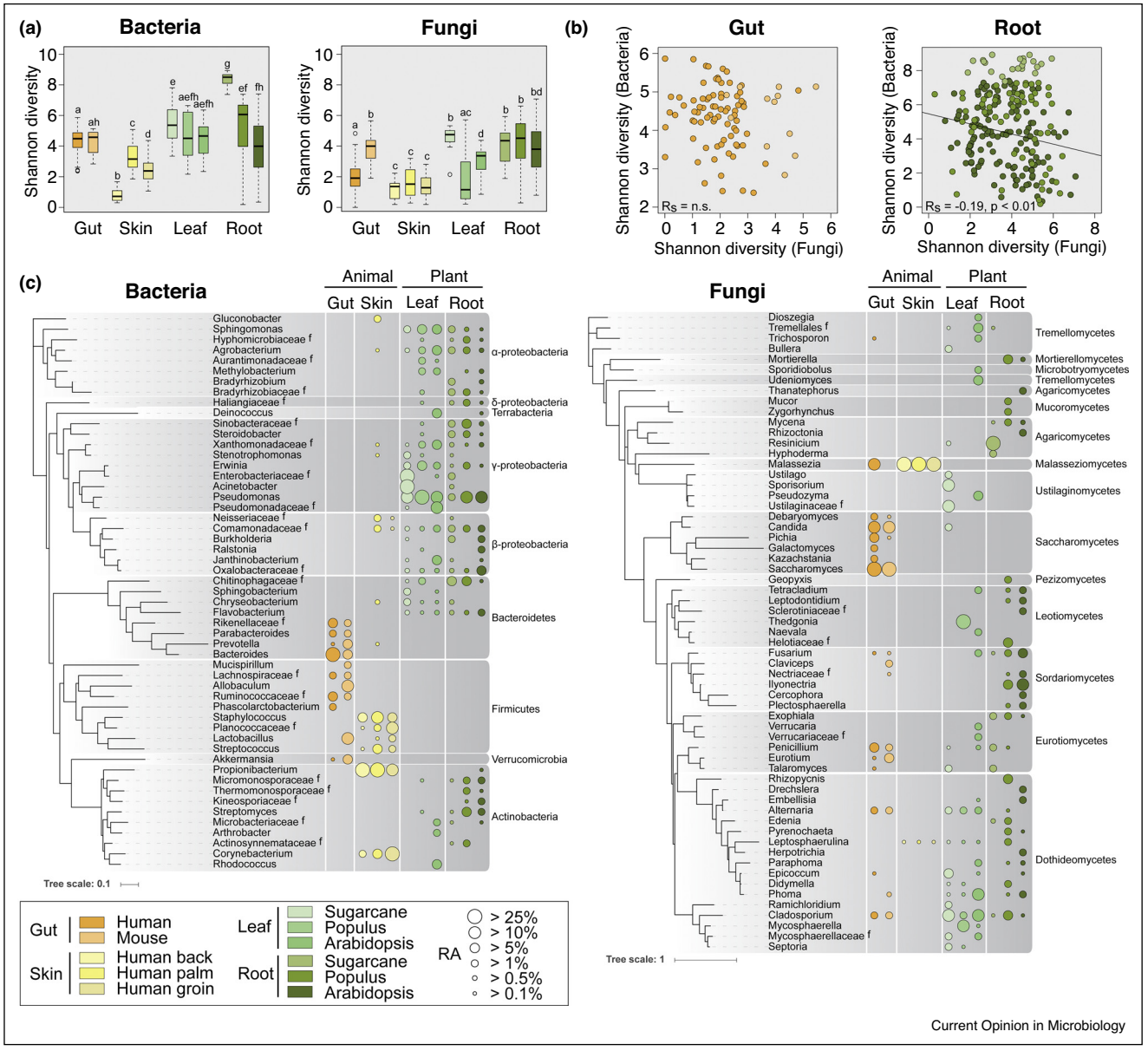
Variation in bacterial and fungal communities across plant and animal niches

To determine the extent to which the host niche drives differentiation and specialization in plant-associated and animal-associated microbial communities, we re-analysed microbial community profiles from seven previous studies that have scrutinized bacterial and fungal community composition in animal gut (i.e. stool samples) and skin habitats [11,31,32], as well as in plant root and leaf endosphere niches [33,34,35••,36]. Microbial profiling based on the 16s rRNA gene (bacteria) and the internal transcribed spacer (ITS, fungi) revealed that bacterial and fungal diversity (Shannon diversity index) is the highest in plant root endosphere samples and the lowest in human skin samples (Figure 1a). Although bacterial alpha diversity is overall similar in stool samples from human, mice, as well as in most endosphere samples from plants, fungal diversity was significantly lower in the human gut, validating the overall reduced taxonomic diversity of the fungal gut microbiota in humans (Figure 1a). Across plant and animal niches, no striking correlation was observed between bacterial and fungal alpha diversity (Figure 1b). Inspection of the most dominant microbial genera detected in these samples (Relative Abundance, RA $>$ 1%) revealed phylogenetic signals in bacterial and fungal community composition across host niches (Figure 1c). Substantial taxonomic overlap was observed between abundant bacterial genera that colonize roots and leaves of the same plant individuals, but also across phylogenetically distant plant species that were harvested from different environments across three continents (*Arabidopsis*: Europe, *Populus*: North America, sugarcane: South America). The overall conserved pattern observed for plant-associated bacteria was less evident for fungi, consistent with the hypothesis that fungi respond to host and environmental variation more extensively than bacteria [36]. Despite some notable differences, similarities in microbial community composition were also observed at the genus level between stool samples of mice and humans, suggesting that similarities in the gut environment between human and mouse drive convergence in microbial community composition at a high taxonomic rank. In contrast, very little taxonomic overlap was observed between the most abundant microbial genera that colonize plant and animal niches, except for few specific fungal genera such as *Cladosporium*, *Alternaria*, *Penicillium*, and *Fusarium* that are shared between gut and plant habitats. The most dominant bacterial and fungal genera include, respectively, *Bacteroides* and *Saccharomyces* in the human gut, *Propionibacterium* and *Malassezia* on human skin surfaces, *Pseudomonas* and *Fusarium* in plant roots, as well as *Pseudomonas* and *Cladosporium* in plant leaves. It is likely that the contrasted environments between gut, skin, and plant endosphere habitats drive microbiota differentiation and niche specialization. Irrespective of the clear taxonomic differentiation observed between host niches in our meta-analysis, it is likely that a substantial functional overlap is retained across these different host-associated microbial communities, as recently described [37,38]. Therefore, functional redundancy between microbiota members, together with functional complementarity between bacteria and fungi is likely key for robust expression of beneficial traits that promote host health across plant and animal systems.

Bacteria-fungi co-occurrence across plant and animal niches

Co-occurrence of bacteria and fungi in particular host niches suggests that microbial cross-kingdom interactions are important selective forces that drive microbial community diversity, variation and stability [39,40]. These cross-kingdom interactions span along the mutualism-parasitism continuum and involve both contact-dependant and contact-independent mechanisms [28]. Network analysis based on amplicon sequencing data of bacterial and fungal communities suggested strong connectivity (i.e. correlation) between abundance of bacterial and fungal taxa in plant and animal niches [20••,35••,41–45]. Both synergistic and antagonistic interactions between bacteria and fungi contribute to microbial community differentiation. Although competitive interactions have been mainly reported between these microbes within host-associated microbiomes [20••,35••,46•,47–49], cooperative interactions (i.e. endosymbiosis, dispersion, cross-feeding) also ubiquitously occur [50–52]. Overall, production of antimicrobials or resource utilization have been described as major forces driving fungal-bacterial balance in host niches [3,27•,53]. Microbiota reconstitution experiments with complex multi-kingdom microbial communities in a gnotobiotic plant system indicated that bacterial root commensals restrict fungal diversity and extensively shape fungal assemblages along the soil-root continuum [20••].

Figure 1



Composition and variation of dominant bacterial and fungal taxa across plant and animal niches. **(a)** Bacterial (left panel) and fungal (right panel) alpha-diversity measured using the Shannon Index across plant and animal niches (Pairwise Wilcoxon test, fdr <0.05). **(b)** Correlation between bacterial and fungal alpha-diversity measured based on the Shannon index is shown for gut (left panel) and root endosphere (right panel) samples. Significance of correlation was tested using Spearman rank correlation. **(c)** Phylogenetic tree of abundant bacterial (left panel) and fungal (right panel) genera colonizing plant and animal niches. Note that family-level classification is shown if the genus is unknown. Relative abundances (RA) were aggregated at the genus (or family) level and are depicted with circles. Only taxa with RA $>1\%$ in at least one of the datasets are shown. Representative sequences of the small subunit ribosomal rRNA or the fungal internal transcribed spacer were used to generate the trees. All datasets were retrieved from the respective repositories and processed according to Ref. [20••], whereas slight changes were necessary to process different data sets. More information and raw data can be obtained by https://github.com/ththi/Interkingdom-Review.

According to this study, filamentous eukaryotes also significantly affected bacterial community composition, but the effect was more subtle [20••]. Therefore, the reciprocal intercommunication between bacteria and fungi likely drive microbial community differentiation, diversity and stability [35••]. In animal guts, antibiotic treatments have been repeatedly associated with overgrowth phenotypes of the fungus *Candida albicans* [25,48,54,55]. For example, a murine model system has been used to assess gut microbiome stability upon long-term exposure to antibiotics. A

drop in bacterial abundance was correlated with an approx. 40-fold increase in *C. albicans* abundance upon antibiotic treatment, which reverted back to normal after cessation of the treatment [54]. Recently, Matsuo *et al.* [56] found that oral applications of β-lactam antibiotics allowed *C. albicans* to colonize the murine gut and resulted in significant reduction in the relative abundance of Clostridiales, Bacteroidales, Enterobacteriaceae and Lactobacillaceae. Faecal transplants from untreated mice into *C. albicans*-colonized mice rapidly restored the endogenous bacterial microbiota and suppressed fungal colonization.

These selected examples suggest that disturbance of bacterial or fungal communities can lead to fungal or bacterial community shifts in host niches. Importantly, this phenomenon is not exclusively explained by direct interactions between bacteria and fungi but can also occur indirectly through modulation of the host immune system by the microbiota [57•,58,59]. Therefore, bacterial-fungal balance is tightly controlled by a two-layered regulatory network that involves both host-microbe and microbe-microbe interactions. Alteration of this balance can be caused by host and microbial genetics, environmental variation (e.g. diet or soil composition), as well as antimicrobial treatments, therefore leading to bacterial-fungal dysbiosis (Figure 2).

Altered bacterial-fungal balance in host diseases

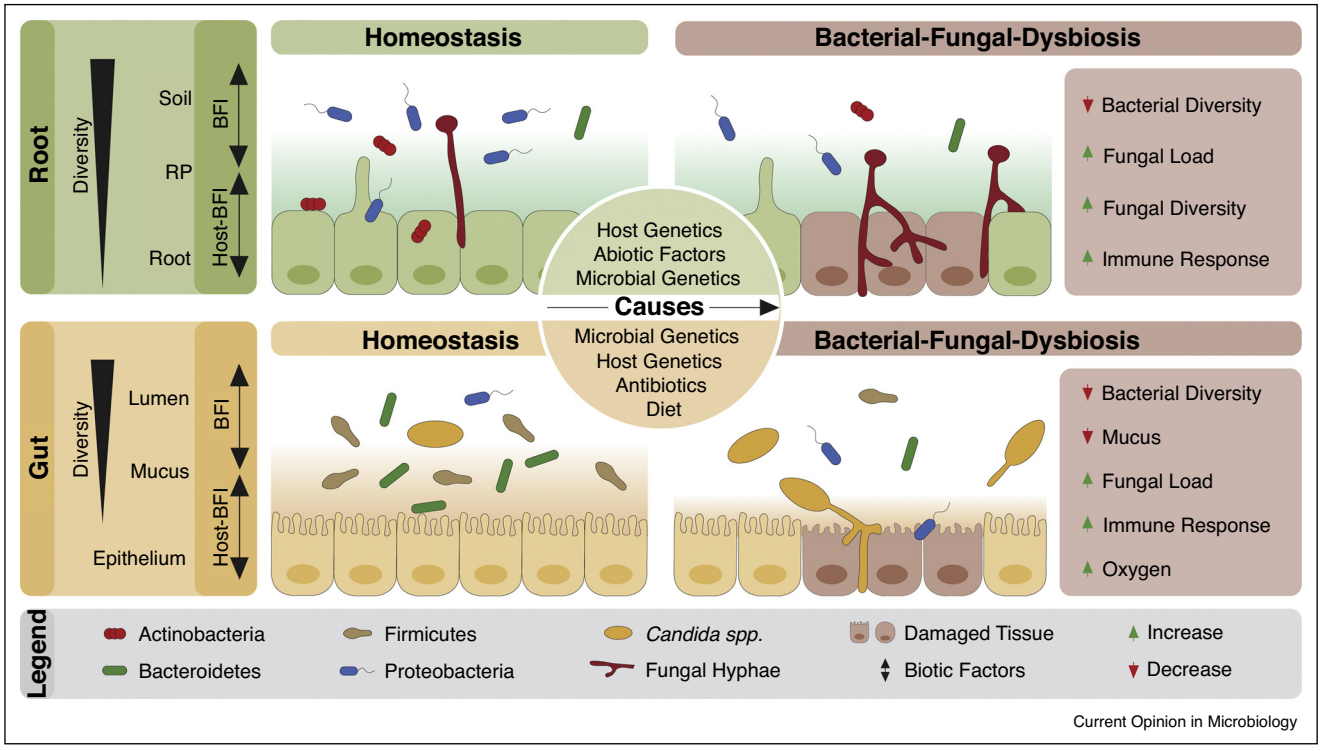
Disease in plants and animals is often associated with shifts in the diversity and composition of the fungal and bacterial microbiota but it remains difficult to experimentally demonstrate that microbial dysbiosis is the cause or the consequence of disease [13,35••,60]. Here, we primarily discuss studies that tested whether alteration of the diversity and composition of bacterial commensals can affect fungal diseases incidence across plant and animal niches (Figure 2). Although, evidence also indicates that host-associated fungi or other filamentous eukaryotes can modulate diversity, abundance and composition of host-associated bacteria [35••,53,61], the physiological relevance for maintaining host-bacterial homeostasis and host health remains poorly described. Therefore, the reciprocal interplay between bacteria and fungi likely contributes to the maintenance of microbial load in host tissues, thereby modulating health and disease states (Figure 2).

In the model plant *Arabidopsis thaliana*, deconstruction of the microbiota into fungal and bacterial culture collections [20••,38] followed by microbiota reconstruction experiments with multi-kingdom synthetic microbial communities and germ-free plants has recently been used to experimentally test whether microbial cross-kingdom interactions affect microbial community structure and plant health. According to this study, numerous root-associated fungi that were isolated from roots of healthy plants were detrimental for the host in the absence of commensal bacteria [20••]. However, co-inoculation with a complex bacterial consortium, as well as with single strains belonging to Pseudomonadaceae or Comamonadaceae families, was sufficient to rescue plant growth in the presence of fungi. Therefore, one major physiological function of the bacterial root microbiota is to control fungal abundance and diversity at the root interface, which maintains fungal homeostasis in roots and promotes host survival [20••]. These findings are supported by further studies, demonstrating direct antagonism of bacterial root commensals towards fungi and providing the foundation for understanding the mechanisms underlying bacteria-mediated fungal disease suppression [3,46•,47,62,63]. Suppression of fungal growth and activity by soil bacterial communities appears to be a general principle that do not only affect soil-borne fungal pathogens but also beneficial arbuscular mycorrhizal fungi, as recently reported [64].

The physiological relevance of bacterial commensals for modulating fungal growth is not restricted to the plant microbiota. In the basal metazoan hydra (*Hydra vulgaris*), a freshwater organism, bacteria residing in the multilayered glycocalyx covering ectodermal epithelial cells are required for protecting hydra polyp from lethal infection by *Fusarium* sp. [27•]. Remarkably, gnotobiotic hydra re-colonized with individual bacteria were not fully protected, whereas those re-colonized with a bacterial consortium (mainly Pseudomonadaceae and Comamonadaceae; Proteobacteria phylum) showed full resistance. This result also illustrates the important contribution of interbacterial interactions for the observed fitness rescue phenotype [27•].

In humans, disturbance of bacterial communities using long-term antibiotic treatments is often associated with fungal overgrowth and is linked to disease outbreak [25,48,54,65]. Particularly, the role of commensal bacteria in regulating *C. albicans* colonization in the gastrointestinal tract has been extensively reported in mice [9,56,66]. Recently, manipulation of mice gut bacteria using specific antibiotics also revealed that bacteria of the family Enterobacteriaceae cooperate with *C. albicans* and promotes their colonization and their active role in intestinal inflammation [67••]. This result illustrates that fungal colonization is affected by specific bacterial taxa in the gut, which modulates health and disease states. Using the same murine system, it has also been shown that the bacterial gut commensal *Bacteroides thetaiotaomicron* is able to subvert *C. albicans* colonization via the activation of gut mucosal immune effectors (HIF-1α, CRAMP), illustrating that inhibition of fungal infection by bacterial commensals can be indirectly mediated by the host [57•].

Figure 2



Bacterial-fungal dysbiosis as a potential cause of disease in plants and animals. In this figure, we illustrate commonalities between plant and animal niches linked to the maintenance of fungal homeostasis by bacterial commensals. Plant roots (green) and animal guts (orange) host multi-kingdom microbial consortia with limited taxonomic overlap. Compartmentalization of the microbiota is observed along the soil-root continuum for plants and along the lumen-epithelium continuum for animals and is associated with a reduced microbial diversity at the vicinity of host cell surfaces. In the homeostatic state, bacterial-fungal (B: bacteria, F: fungi) balance is maintained by both host-microbe (Host-BFI) and microbe-microbe (BFI) interactions. In plant roots, Proteobacteria were reported as important microbiota members controlling fungal load and diversity in plant roots, whereas Bacteroidetes and Firmicutes were reported to fulfil this function in the human gut. Physiological changes associated with bacterial-fungal dysbiosis are indicated on the right.

Conclusions

We suggest a general model in which bacterial commensals can alter fungal diversity and abundance directly through microbial competition and indirectly through modulation of the host immune system. The relevance of bacterial commensals for restricting fungal diversity and abundance in host niches implies that plants and animals may equally rely on their immune system and their endogenous bacterial microbiota to maintain fungal balance in host tissues. Given the little overlap between the dominant bacterial taxa colonizing plant and animal surfaces (Figure 1c), it is likely that distinct bacterial lineages modulate fungal balance across different host niches [20••,27•,63]. Although the molecular mechanisms are likely different, the conserved protective functions conferred by bacterial commensals in plant and animal niches suggest functional trait convergence across host-associated microbiomes. The reciprocal effect of fungi on bacteria is also expected to maintain homeostatic relationship between the bacterial microbiota and the host, therefore implying that fungal-bacterial balance is controlled in both directions. Therefore, we propose that the interplay between bacteria, fungi and their hosts is critical for maintaining total microbial load in host tissues. This reciprocal cross-kingdom regulation is likely a driving force that contributes to the establishment of diverse multi-kingdom microbial consortia that promote plant and animal health. Further research is required to systematically dissect the respective underlying mechanisms in order to identify microbes that control bacterial-fungal balance and can be used for agronomic or therapeutic applications. Particularly, microbes that extensively affect bacterial-fungal balance via multiple control points represent potential keystone taxa that might modulate health and disease across plant and animal kingdoms.

Conflict of interest statement

Nothing declared.

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