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REVIEW ARTICLE

Bacterial–fungal interactions: ecology, mechanisms and challenges

Aurélie Deveau[1,*], Gregory Bonito[2], Jessie Uehling[3,4], Mathieu Paoletti[5], Matthias Becker[6], Saskia Bindschedler[7], Stéphane Hacquard[9], Vincent Hervé[7,8,†], Jessy Labbé[10,11], Olga A. Lastovetsky[12,‡], Sophie Mieszkin[1], Larry J. Millet[13], Balázs Vajna[14], Pilar Junier[7], Paola Bonfante[15], Bastiaan P. Krom[16], Stefan Olsson[17], Jan Dirk van Elsas[18] and Lukas Y. Wick[19]

[1]Université de Lorraine, INRA, UMR IAM, 54280 Champenoux, France, [2]Department of Plant Soil and Microbial Sciences, Michigan State University, East Lansing, MI 48824, USA, [3]Biology Department, Duke University, Box 90338, Durham, NC 27705, USA, [4]Plant and Microbial Biology, University of California, Berkeley, CA 94703, USA, [5]Institut de Biologie et Génétique Cellulaire, UMR 5095 CNRS et Université de Bordeaux, 1 rue Camille Saint-Saëns, 33077 Bordeaux cedex, France, [6]IGZ, Leibniz-Institute of Vegetable and Ornamental Crops, 14979 Großbeeren, Germany, [7]Laboratory of Microbiology, Institute of Biology, University of Neuchâtel, CH-2000 Neuchâtel, Switzerland, [8]Laboratory of Biogeosciences, Institute of Earth Surface Dynamics, University of Lausanne, CH-1015 Lausanne, Switzerland, [9]Department of Plant Microbe Interactions, Max Planck Institute for Plant Breeding Research, 50829 Cologne, Germany, [10]Biosciences Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831, USA, [11]Department of Biochemistry and Cellular and Molecular Biology, University of Tennessee, Knoxville, TN 37996, USA, [12]Graduate Field of Microbiology, Cornell University, Ithaca, NY 14853, USA, [13]Joint Institute for Biological Science, University of Tennessee, and the Biosciences Division of Oak Ridge National Laboratory, Oak Ridge, TN 37831, USA, [14]Department of Microbiology, Eötvös Loránd University, Pázmány Péter sétány 1/C, 1117 Budapest, Hungary, [15]Department of Life Science and Systems Biology, University of Torino, 10125 Torino, Italy, [16]Department of Preventive Dentistry, Academic Centre for Dentistry, G. Mahlerlaan 3004, 1081 LA, Amsterdam, The Netherlands, [17]State Key Laboratory of Ecological Pest Control for Fujian and Taiwan Crops, Fujian Agriculture and Forestry University (FAFU), Fuzhou 350002, China, [18]Microbial Ecology group, GELIFES, University of Groningen, 9747 Groningen, The Netherlands and [19]Helmholtz Centre for Environmental Research—UFZ, Department of Environmental Microbiology, Permoserstraße 15, 04318 Leipzig, Germany

*Corresponding author: Université de Lorraine, INRA, UMR IAM, 54280 Champenoux, France. Tel: +33-3-83-39-40-88; Fax: +33-3-83-39-40-69; E-mail: aurelie.deveau@inra.fr

†Present address: Department of Biogeochemistry, Max Planck Institute for Terrestrial Microbiology, 35043 Marburg, Germany

‡Present address: School of Biology and Environmental Science, University College Dublin, Dublin, Ireland.

One sentence summary: Bacterial–fungal interactions are cornerstones of numerous processes that impact ecosystem functions, animal and plant physiology, and industrial activities.

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†Vincent Hervé, http://orcid.org/0000-0002-3495-561X

ABSTRACT

Fungi and bacteria are found living together in a wide variety of environments. Their interactions are significant drivers of many ecosystem functions and are important for the health of plants and animals. A large number of fungal and bacterial families engage in complex interactions that lead to critical behavioural shifts of the microorganisms ranging from mutualism to antagonism. The importance of bacterial–fungal interactions (BFI) in environmental science, medicine and biotechnology has led to the emergence of a dynamic and multidisciplinary research field that combines highly diverse approaches including molecular biology, genomics, geochemistry, chemical and microbial ecology, biophysics and ecological modelling. In this review, we discuss recent advances that underscore the roles of BFI across relevant habitats and ecosystems. A particular focus is placed on the understanding of BFI within complex microbial communities and in regard of the metaorganism concept. We also discuss recent discoveries that clarify the (molecular) mechanisms involved in bacterial–fungal relationships, and the contribution of new technologies to decipher generic principles of BFI in terms of physical associations and molecular dialogues. Finally, we discuss future directions for research in order to stimulate synergy within the BFI research area and to resolve outstanding questions.

Keywords: bacterial–fungal interactions; metaorganisms; microbiome; mechanism; microbial logistics

INTRODUCTION

Bacteria and fungi often share microhabitats where they assemble into dynamic co-evolving communities. Such bacterial–fungal communities have been described to exist in nearly all ecosystems and include microbial species from a wide diversity of fungal and bacterial families (Peleg, Hogan and Mylonakis 2010; Scherlach, Graupner and Hertweck 2013). Interactions between fungi and bacteria play a key role in the functioning of numerous ecosystems: they are cornerstone members of communities driving biochemical cycles, and contribute to both the health and diseases of plants and animals (Fig. 1). Moreover, bacteria and fungi have been exploited by humans for centuries to manufacture food products, antibiotics and secondary metabolites for pharmacology and biotechnological applications (Frey-Klett *et al.* 2011). As a consequence, by-products of bacterial–fungal interactions (BFI) have been harnessed to improve many human activities in agriculture, horticulture, forestry, environmental protection, food processing, biotechnology and medical applications.

BFI intrinsically modulate the behaviour of either or both of the interacting partners. Such modulation cannot be easily predicted based on our knowledge of the biology of the isolated microorganisms grown in pure cultures. Different levels and degrees of specificity of BFI have been reported. On one end of the spectrum, co-occurrence patterns of bacteria and fungi result from intimate biophysical and metabolic interactions during which bacterial and fungal partners interdependently develop and co-evolve. On the other end, co-occurrence may not be representative of any causal relationships, being the result of stochastic 'mixing' within the microbial community. Depending on the degree of interaction, the molecular dialogue between the partners may be very simple, highly refined or absent. Depending on the species involved in BFI, interactions can be highly specific, like the intimate interaction between endofungal bacteria and early emerging fungi (Bonfante and Desirò 2017), or they can involve a broad spectrum of species. For instance, the opportunistic human pathogens *Candida albicans* and *Pseudomonas aeruginosa* frequently interact with each other, but also with numerous additional bacteria and fungi, respectively (Leclair and Hogan 2010). Such multipartner interactions can occur within a single environment—such as in the oral plaque (Janus, Willems and Krom 2016), in soil (Warmink, Nazir and van Elsas 2009), in a single food product (Kastman *et al.* 2016) or across multiple environments. Opportunistic microorganisms such as the aforementioned *P. aeruginosa* colonise a wide variety of environments including human tissues, plant root systems and soils, in which they engage in different interactions with local fungal species (Walker *et al.* 2004). Whatever the environment considered, BFI can produce a diverse range of interactions—from antagonism to mutualism—that influence the biology and ecology of the fungal and bacterial partners at different levels, i.e. with respect to growth, reproduction, transport/movement, nutrition, stress resistance and pathogenicity. The outcomes of these interactions are the combined results of the physical associations (biofilm, free cells, intracellular), the molecular dialogue between the organisms (direct or indirect), and the environmental conditions and/or the host activity (Fig. 1).

Within the past decade, a range of multidisciplinary studies on diverse BFI, which integrate tools from molecular biology, genomics, chemical and microbial ecology, biophysics and ecological modelling, have emerged. The more than 300 studies dealing with BFI, as published within the last five years across divergent fields of research (e.g. medicine, agriculture, environment science, biotechnology and food processing), have culminated in a better understanding of interaction mechanisms and consequences of BFI. Striking mechanistic generalities have emerged that extend beyond known BFI despite the intricacies inherent to each system analysed, as first outlined by Frey-Klett *et al.* (2011) and Scherlach, Graupner and Hertweck (2013). Such generalist patterns mirror the remarkable similarities shared between plants and animals recently documented in microbiota-assisted host nutrition (Hacquard *et al.* 2015). Here, we review the main findings obtained with respect to BFI in different fields in the past years, including the latest advances with respect to the roles and mechanisms involved, as well as the emerging opportunities and applications to biotechnology and ecology.

Figure 1. Relevance, applications and drivers of BFI. Biotic and abiotic environments filter microbial communities selecting for specific consortia, and conversely interactions between microorganisms influence the biotic and abiotic environment. Bacterial–fungal phenotypes emerge from physical and molecular interactions between members of the microbial community and are highly dependent on time and scale.

BFI WITHIN COMPLEX NETWORKS OF INTERACTIONS: FROM FUNGAL MICROBIOMES TO METAORGANISMS AND HOLOBIONTS

The exponential development of molecular tools aimed at describing the diversity of microorganisms in many biomes and environments on Earth has brought to light the huge diversity of microorganisms and potential interactions between them (Thompson *et al.* 2017). As a consequence, the traditional concept of BFI as bipartite bacterial–fungal or bacterial–fungal–host interactions is now shifting towards BFI as complex networks of multiple interacting organisms. In these networks, there may be different levels of complexity depending on the environment and the scale of analysis. The networks can be envisioned at different levels depending on the habitats considered: ranging from networks restricted to microorganisms on abiotic matrices and surfaces such as soils, wood, hydrothermal vents, water pipes and medical catheters (Hervé *et al.* 2014; Lindsay and Hogan 2014; Urich *et al.* 2014; Douterelo *et al.* 2016; de Menezes, Richardson and Thrall 2017) to networks involving higher organisms, in which BFI occur within the microbiomes of hosts such as lichens (Grube *et al.* 2015), corals (Moree *et al.* 2013), nematodes (Wang *et al.* 2014), insects (Aylward *et al.* 2014), batrachians (Longo and Zamudio 2017) or mammals (Hacquard *et al.* 2015; Hoyt *et al.* 2015). In this regard, the interacting microorganisms together may be conceptually regarded as one metaorganism (Olsson, Bonfante and Pawlowska 2017, see box 1).

The fungal microbiome

The hyphosphere (box 1) provides microhabitats that are colonised by specific bacterial communities (Frey-Klett *et al.* 2011). In a seminal paper, some bacterial associates of soil fungi were called bacterial 'fungiphiles' (Warmink and van Elsas 2009, box 1). The diversity of these communities can range from a few to several hundreds of species, depending on the fungus and the organ considered (Grube *et al.* 2015; Wolfe and Dutton 2015; Schulz-Bohm *et al.* 2016; Ghodsalavi *et al.* 2017). Filamentous fungi can produce differentiated tissues (e.g. mycelium, fruiting bodies, spores, mycorrhizae) that are colonised by distinguished sets of microbiomes (Zagriadskaia *et al.* 2013; Deveau *et al.* 2016; El-Jurdi and Ghannoum 2017). While some bacteria, such as *Burkholderia* spp., can colonise a large set of fungal species given their abilities to utilise fungal-derived metabolites and overcome fungal defence mechanisms (Haq *et al.* 2014; Stopnisek *et al.* 2016; Jung *et al.* 2018), others may have a more specific and intimate relationship with their fungal hosts (Warmink, Nazir and van Elsas 2009). Similar to plant and animal microbiomes, which are known to contribute to the 'extended phenotype' of their hosts, it is likely that fungal microbiomes also contribute to the biology of their fungal hosts. Indeed, treatments with antibiotics that suppress or alter fungal-associated bacterial communities impaired mycelial growth, secondary metabolite production and/or reproduction (Vahdatzadeh, Deveau and Splivallo 2015; Schulz-Bohm *et al.* 2016; Mondo *et al.* 2017; Uehling *et al.* 2017).

Box 1. Definitions of terms and concepts

Bacterial fungiphile. Bacterial strain that preferentially associates with fungi and for which the hyphosphere is the main habitat (Warmink and van Elsas 2009).
Hub microorganism. Highly interconnected species that drives community responses through microbe-microbe interactions.
Hyphosphere. The microhabitat surrounding hyphal cells.
Keystone species. Species on which relies the functioning of the community.
Metaorganism & holobiont. The metaorganism concept has been defined as "a community of interacting biological entities that is indicated by a metagenome" (Bosch and McFall-Ngai 2011). It thus is a dynamic entity in dependency of the boundaries set by the researchers. Similarly, the holobiont concept is often used in reference to microbiomes associated with hosts, being both parts of this association subjected to evolutionary selection (Bordenstein and Theis 2015). When it comes to microbial interactions, it is often difficult to determine who is the "host", as is the case in, for example, the fungal-algal-bacterial holobiont (Aschenbrenner *et al.* 2016). Here, we redefine a holobiont as a "unit of biological organization composed of several distinct genomes, that, in principle, influence the genomic evolution of each other". This definition is "host neutral", and avoids the inclusion of temporary opportunistic assemblages, while at the same time focusing on the evolutionary importance of the holobiont concept (Bordenstein and Theis 2015).
Microbial logistics. Effective provision of microbes, matter and energy for microbial ecosystem functioning and targeted substrate turnover (Fester 2014).
-omics. The suffix "omics" designates an approach that permits to study given molecules in their globality within a sample: metabolomics for metabolites, proteomics for proteins, volatilomics for volatiles, genomics for genes and transcriptomics for transcripts. Moreover, adding the prefix 'meta' implies that the omics method will, within technical limits, measure all genes, transcripts, proteins, metabolites and volatiles in a given sample containing more than one organism.

Understanding of the fungal microbiome is an important challenge in food processing and production, as microbiomes are often involved in fermentation of alcoholic beverages (e.g. wine and beers), dairy products (e.g. cheese, sourdough) and other fermented foods (for review, see Wolfe and Dutton 2015), as well as cultivation of edible mushrooms (Bánfi *et al.* 2015; Murat 2015).

The endofungal microbiome

Bacteria that live inside fungal cells (i.e. endofungal bacteria or endobacteria) have first been described in the seminal work by Barbara Mosse (Mosse 1970). They were originally considered as biological curiosities; however, numerous emerging studies have demonstrated their omnipresence in fungi, as well as their clear effects on fungal biology (Bonfante and Desirò 2017). To date, endobacteria have been reported in fungi with diverse lifestyles and of broad taxonomic origins, including endophytic Ascomycetes (Hoffman and Arnold 2010; Arendt *et al.* 2016; Shaffer *et al.* 2016), symbiotic, pathogenic and endophytic Basidiomycetes (Bertaux *et al.* 2003; Ruiz-Herrera *et al.* 2015; Glaeser *et al.* 2016) as well as saprotrophic and symbiotic fungi in the Mucoromycota (Partida-Martínez 2017; Uehling *et al.* 2017; Desirò *et al.* 2018). The best-studied fungal endobacteria belong to the family Burkholderiaceae, and are associated with early-diverging lineages of terrestrial fungi within the Mucoromycota (Bonfante and Desirò 2017; Uehling *et al.* 2017). These associations appear to be specific, and have presumably tightly co-evolved over millions of years (Mondo *et al.* 2012; Desirò *et al.* 2015; Uehling *et al.* 2017). This has resulted in host dependency and significant genome reductions for the bacterial endosymbionts (Ghignone *et al.* 2012; Uehling *et al.* 2017). Endobacteria can have profound effects on fungal host biology, including aspects of host reproduction (Partida-Martinez *et al.* 2007; Mondo *et al.* 2017), growth (Shaffer *et al.* 2017; Uehling *et al.* 2017; Desirò *et al.* 2018), energy dynamics (Salvioli *et al.* 2016; Vannini *et al.* 2016), primary metabolism (Lastovetsky *et al.* 2016; Salvioli *et al.* 2016; Vannini *et al.* 2016; Li *et al.* 2017; Uehling *et al.* 2017) and secondary metabolism (Rohm *et al.* 2010; Hoffman *et al.* 2013).

Several examples of fungi in the Mucoromycota and their endobacteria offer lessons in fungal endobacterial biology. First, the association between *Paraburkholderia rhizoxinica* (formerly *Burkholderia rhizoxinica*) and *Rhizopus microsporus* is mutualistic, whereby the bacterium provides its host with a toxin, which facilitates fungal pathogenicity on rice. Remarkably, the vertically transmitted endobacteria impact fungal reproduction, as their removal abolishes asexual sporulation and significantly reduces mating (Mondo *et al.* 2017). A recent study leveraged this endobacterial control over fungal mating into identifying reproductive genes in the Mucoromycota, a group of fungi that is notoriously recalcitrant to genetic approaches, as well as reconstructing key reproductive pathways across the fungal kingdom (Mondo *et al.* 2017). Moreover, studying the pre-symbiotic interaction between *R. microsporus* and *Paraburkholderia* revealed that the fungus undergoes specific lipid metabolic changes in order to accommodate endobacteria, which, when perturbed, shift the interaction from mutualistic into antagonistic (Lastovetsky *et al.* 2016). Clearly, the *Rhizopus-Paraburkholderia* system is a token of the key role that bacteria can play in modulating the basic biology of their host fungi.

A second example of a well-studied endobacterial-fungal system is the association between members of the arbuscular mycorrhizal fungal family (Gigasporaceae, Glomeromycotina) and *Candidatus* Glomeribacter gigasporarum (*Ca*Gg, Burkholderiaceae). These bacteria are vertically transmitted between the fungal generations (Bianciotto *et al.* 2004) and have a strong effect on the pre-symbiotic phase of the fungus. In the pre-symbiotic phase, they raise the fungal bioenergetic capacity, increase ATP production and elicit reactive oxygen detoxification mechanisms (Salvioli *et al.* 2016). Recent work discovered a new aspect of the endobacterial biology, in that a toxin-antitoxin system was active (Salvioli Di Fossalunga *et al.* 2017), as well as the whole operon for vitamin B_{12} production (Ghignone *et al.* 2012). This indicates potential metabolic assistance by the endobacterium, not only for the fungal host, but also for the plant mycorrhizal partner. Interestingly, sharing of B-vitamins was also described for the lichen *Lobaria pulmonaria*, where lichen-associated bacteria have been hypothesised to support photosynthesis by provision of vitamin B_{12} (Grube *et al.* 2015).

A third fungal endosymbiont example is the endobacterium *Mycoavidus cysteinexigens*, an endosymbiont of the saprotrophic fungus *Mortierella elongata* (Mortierellomycotina) (Uehling *et al.* 2017). Despite the close phylogenetic affiliation to *Ca*Gg, its impact on host fungal growth is strikingly different. *Ca*Gg promotes the growth of its fungal host, while *M. cysteinexigens* decreases

fungal growth (Uehling *et al.* 2017) suggesting that these later endobacteria utilise host fungal metabolic products. This behaviour likely reflects their ancient divergence from *Ca*Gg and co-evolution with the fungal host.

Interestingly, many Mucoromycota, including Glomeromycotina, Endogone and Mortierellamycotina, can host endosymbionts belonging to the Mollicutes group of bacteria (Naumann, Schüssler and Bonfante 2010; Desirò *et al.* 2014, 2015, 2018); some have been identified as novel types named '*Candidatus* Moeniiplasma glomeromycotorum' (*Ca*Mg) (Naito *et al.* 2017). The effect of these Mollicutes endobacteria on their fungal hosts is still being unraveled. Molecular evolution analyses of Glomeromycotina indicate that *Ca*Mg is a parasite of the fungus. Experimental work with Mortierellamycotina indicates that the Mollicutes-related endosymbionts are conditional parasites (Toomer *et al.* 2015; Desirò *et al.* 2018). Remarkably, genome sequencing of selected *Ca*Mg revealed evidence of horizontal gene transfer events, in particular of fungal genes involved in post-translational modification (Naito, Morton and Pawlowska 2015; Torres-Cortés *et al.* 2015). Ongoing studies now aim at determining the function of *Ca*Mg; in particular, the striking observation of the presence of multiple lineages of endobacteria within a single fungal host calls for further scrutiny (Desirò *et al.* 2014).

In contrast to the endobacteria of Mucoromycota, endofungal bacteria reported in the Ascomycota and Basidiomycota appear to be more transient in nature, yet they can also influence host phenotype and fitness (Hoffman and Arnold 2010; Spraker *et al.* 2016). Such transient bacterial–fungal associations may be ecologically important in local habitat-associated adaptation, in which the fungal hosts may serve as environmental reservoirs or refuges for the bacteria (Spraker *et al.* 2016).

The mechanisms by which endofungal bacteria colonise their hosts have been deciphered for only a few examples. *Paraburkholderia rhizoxinica* actively secretes chitinolytic enzymes by means of the type II secretion system, to penetrate the hyphae of the *R. microsporus* host (Moebius *et al.* 2014). In contrast, *Ralstonia solanacearum* requires the production of the lipopeptide ralsomycin to invade the chlamydospores of its fungal hosts (Spraker *et al.* 2016). Once inside the mycelium, some bacteria, much like mitochondria, are able to move through dolipore septa (Bertaux *et al.* 2005). Some can also be vertically transmitted between generations through fungal spores (Spraker *et al.* 2016), with the bacterial type III secretion system possibly playing a role (Lackner, Moebius and Hertweck 2011). Further studies are necessary to decipher how widespread these mechanisms are among the endofungal bacteria. Interestingly, in some cases endosymbionts influence fungal host biology and the ability of the fungus to interact with its own host through beneficial (Hoffman *et al.* 2013; Vannini *et al.* 2016; Guo *et al.* 2017) or detrimental (Lackner and Hertweck 2011) associations, giving rise to multilevel interkingdom interactions.

Bacterial DNA is often detected in fungal genome-sequencing projects, opening the question of whether endobacteria are more common in fungi than previously thought. Such 'contaminating' DNA could belong to external bacteria or to endobacteria (either transient or stable). With improvements in genome-sequencing technology, it has become possible to assemble entire bacterial genomes from a fungal–bacterial DNA preparation (Uehling *et al.* 2017). Researchers are urged to keep an open mind to the possibility of endobacterial associates in their fungi before discarding these 'contaminating' bacterial reads from their projects. Although presence of bacterial reads in fungal sequencing projects is indicative of potential endobacterial symbionts, the presence and taxonomic identity of endofungal bacteria should still be demonstrated by other evidence, such as provided by transmission electron microscopy and fluorescence *in situ* hybridisation (FISH).

BFI in complex microbial communities, metaorganisms and holobionts

Despite the increasing number of in-depth analyses of microbial communities in multiple systems, studies that consider fungi and bacteria together are still limited in number. Clearly, Next Generation Sequencing (NGS) offers unprecedented opportunities for obtaining a broad view of potential BFI across habitats (reviewed in de Menezes, Richardson and Thrall 2017), yet it only permits co-occurrence inferences that may not represent true interactions. Network inference can help to identify those microbes that potentially interact. In a recent study, co-occurrence analyses between bacterial and fungal OTUs across 266 soil samples revealed a significant association between bacteria belonging to the genus *Burkholderia* and a wide range of soil fungi (Stopnisek *et al.* 2016). This ubiquitous association, together with co-cultivation experiments under laboratory conditions, suggests that specific soil bacteria have evolved strategies to utilise fungal-secreted metabolites and overcome fungal defence mechanisms (Stopnisek *et al.* 2016). Interactions involving hub microorganisms or keystone species (box 1) can be then further investigated at the molecular level. Agler and co-workers thus identified the yeast *Dioszegia* as a fungal hub of the phyllosphere microbiome of *Arabidopsis thaliana*, as well as its bacterial interactants (Agler *et al.* 2016). This methodology has already identified BF networks and the drivers that govern community assembly in leaf litter (Purahong *et al.* 2016), soils (de Menezes *et al.* 2014; Ma *et al.* 2016; Stopnisek *et al.* 2016), floral nectar (Álvarez-Pérez and Herrera 2013), plants (Bell *et al.* 2014; Agler *et al.* 2016) and human microbiomes (Mukherjee *et al.* 2014; Trosvik and de Muinck 2015). All these studies revealed non-random associations between fungi and bacteria and an over-representation of positive associations compared to negative ones. Such positive associations are likely to reflect commonalities of habitats between the microorganisms and potential positive interactions. However, they can also be the result of the common colonisation of a habitat via the same selective or dispersal agent, as in the case of some microorganisms in flowers that are transported by bees (Álvarez-Pérez and Herrera 2013). Networks can vary from a few dozens of microorganisms (as in the oral microbiome) to over 50.000 (in soil) (Mukherjee *et al.* 2014; Ma *et al.* 2016). Linking network-inferred prediction with functional analyses will represent an important step forward to decipher the potential link between BFI and ecosystem functioning (Ma *et al.* 2016; Purahong *et al.* 2016). For instance, the co-occurrence of the lignocellulose decomposer fungi *Clitocybe* and *Mycena* spp. with potential N2-fixing bacterial taxa was correlated with nitrogen (N) deposition in the soil during the decay of leaves, indicating that some bacteria may contribute to the N nutrition of fungi while fungi make C available for bacteria (Purahong *et al.* 2016).

An ecological balance within the microbiome and between the microbiome and the host (host–microbiota homeostasis) has been hypothesised to be fundamental to maintaining the health of both animal and plant hosts (Krom and Oskam 2014; Hacquard *et al.* 2017). Understanding how microbiomes shift between healthy symbiosis and unhealthy dysbiosis, and how BFI are involved in such process, is therefore of rising interest in many research fields. For example, BFI can be a factor that

modulates human disease if the ecological balance between the partners shifts. This is illustrated by the recurrent interactions between fungi and bacteria in infections of burn wounds, denture stomatitis, lungs of cystic fibrosis and immunocompromised patients, as well as in (recurrent) bowel disease, or related to the use of invasive medical devices (Dhamgaye, Qu and Peleg 2016; Förster *et al.* 2016). Consequently, BFI in such associations may impact the virulence of both partners of the interactome. In plants, the critical role of the microbiota for suppression of plant pathogens has been extensively reported (e.g. Santhanam *et al.* 2015; Ritpitakphong *et al.* 2016; Expósito *et al.* 2017). Similar to what has been described for human diseases, several plant infections are often associated with dysbiosis and the loss of diversity in the microbiome (Santhanam *et al.* 2015; Koskella, Hall and Metcalf 2017). The mechanisms leading to bacterial–fungal homeostasis in plant tissues remain unclear, but likely involve a combination of host-dependent and host-independent mechanisms, such as metabolic and nutritional interdependencies among microbes, secretion of antimicrobials and production of protective barriers (Wei *et al.* 2015; Mousa *et al.* 2016).

Such complex interactions are starting to be taken into account when designing new strategies to improve the growth and health of crops (Panke-Buisse *et al.* 2015; Poudel *et al.* 2016), or treating dysbiosis in animals and plants using microbiome-based strategies (Fraune *et al.* 2015; Santhanam *et al.* 2015; Adam *et al.* 2016). For instance, there is growing awareness that we now need to consider potential synergisms between BF pathogenic communities in order to analyse and treat diseases (Lamichhane and Venturi 2015), with an emphasis on the interactions between microorganisms in the context of pathogenesis (Lopes, Azevedo and Pereira 2014). In addition, positive BFI effects on human health might allow to use fungi and/or bacteria as probiotics. Microbiome-based analyses are also used to improve food processes such as cheese or wine making (Pinto *et al.* 2014; Dugat-Bony *et al.* 2015; Liu *et al.* 2017), and could be applied to many other systems including energy production and bioremediation.

The emerging importance of Archaea among microbiomes

Besides bacteria, Archaea are now also recognised as important members of Earth's biosphere in terms of their contribution to ecosystem functioning (Moissl-Eichinger *et al.* 2017). They play key roles in global carbon and nitrogen cycles, for instance in methanogenesis, anaerobic methane oxidation (methanotrophy) and ammonia oxidation. Interestingly, Archaea are found in niches where BFI occur, such as decaying wood (Rinta-Kanto *et al.* 2016), the mycorrhizosphere (Bomberg and Timonen 2009), rhizosphere (Thion *et al.* 2016), soil (Ma *et al.* 2016), rumen (Kumar *et al.* 2015) and human gut (Hoffmann *et al.* 2013). However, to date, only few studies have investigated the bacterial–archaeal (Raymann *et al.* 2017), archaeal–fungal (Hoffmann *et al.* 2013; Kumar *et al.* 2015) and fungal–bacterial–archaeal (Ma *et al.* 2016) interactions or co-occurrences. Altogether, this suggests that Archaea should be integrated into the metaorganism concept, especially since they are known to be involved in different microbial interactions including syntrophy (Morris *et al.* 2013).

MECHANISMS OF INTERACTION

A suite of molecular mechanisms may underlie BFI in different systems relying on a combination of physical and chemical interactions, as outlined in Frey-Klett *et al.* (2011) and illustrated in Table S1, Supporting Information. Such mechanisms were conceptually divided into four classes, i.e. (i) antibiosis involving metabolite exchange, (ii) signalling and chemotaxis involving metabolite sensing and conversion, (iii) physicochemical changes following adhesion and (iv) protein secretion. Clearly, the above division in four mechanistic types allows for overlap, as it is likely that in all four cases signalling, signal perception and modulation of gene expression in either or both of the partner organisms play a crucial role. Hence, we present a strong focus on the ways by which BFI depend on signal (or metabolite) exchange. We also focus specifically on recent advances on physical interactions during BFI and the particular importance of 'microbial logistics' in BFI.

Signalling and recognition during BFI

Whether and to what extent fungi and bacteria have the ability to perceive and recognise other microorganisms is a question that animates the BFI field for years. Transcriptomic analyses of several BFI have demonstrated that both fungi and bacteria react to the presence of the partner microorganism and respond differentially depending on the interacting partners (e.g. Mela *et al.* 2011; Sztajer *et al.* 2014; Gkarmiri *et al.* 2015; Haq *et al.* 2017; Tomada *et al.* 2017). Several cues may be used by the microorganisms for mutual detection, and most are based on small signalling molecules (Scherlach and Hertweck 2017) (Fig. 2). The underlying modes of action vary as well as specificity; from highly specific signals which are solely perceived as a direct sign of the presence of the interacting partner, to compounds that interfere with signalling pathways in the interacting partner and induce a specific response. This second class of compounds is the most reported one in the literature so far.

One example is quorum sensing (QS). QS has long been considered to constitute a means by which bacteria sense and communicate their population density to coordinate their activities. Recently, QS was shown to be also involved in fungal processes such as morphogenesis, germination, apoptosis, pathogenicity and biofilm development (reviewed in Wongsuk, Pumeesat and Luplertlop 2016). Furthermore, both bacterial and fungal QS molecules were shown to play significant roles in cross-kingdom signalling (Cugini *et al.* 2007; Stanley *et al.* 2014; Sztajer *et al.* 2014; Dixon and Hall 2015). Indeed, certain bacteria react to fungal QS molecules (e.g. farnesol, tyrosol, phenylethanol, tryptophol; Wongsuk, Pumeesat and Luplertlop 2016), and, conversely, fungi may react to bacterium-secreted compounds (e.g. quinolone signals, homoserine lactones; Dixon and Hall 2015; Fourie *et al.* 2016). Such interkingdom signalling is likely to be a common mechanism of communication between microbes in mixed fungal-bacterial biofilms in which these molecules are abundantly produced (Trejo-Hernández *et al.* 2014; Dixon and Hall 2015; Fourie *et al.* 2016). This intricate dialogue has been particularly well studied in *C. albicans–P.aeruginosa/S. gordonii/S. aureus* interactions (Lindsay and Hogan 2014). Signalling may be involved in a broader number of habitats since QS may also intervene in bacterial endofungal symbioses (Kai *et al.* 2012).

Other soluble compounds released by fungi are also sensed by bacteria. Examples are organic acids, sugars, polyols and even toxins. These compounds induce bacterial chemotaxis towards the hyphae of fungi that excrete them. Among these compounds, oxalic acid is of peculiar interest since it induces chemotaxis in the soil bacterium *Collimonas* without being consumed (Rudnick, van Veen and de Boer 2015; Haq 2016). This is in contrast to most other compounds (e.g. glycerol) that are later used as a source of nutrients by fungal-associated bacteria

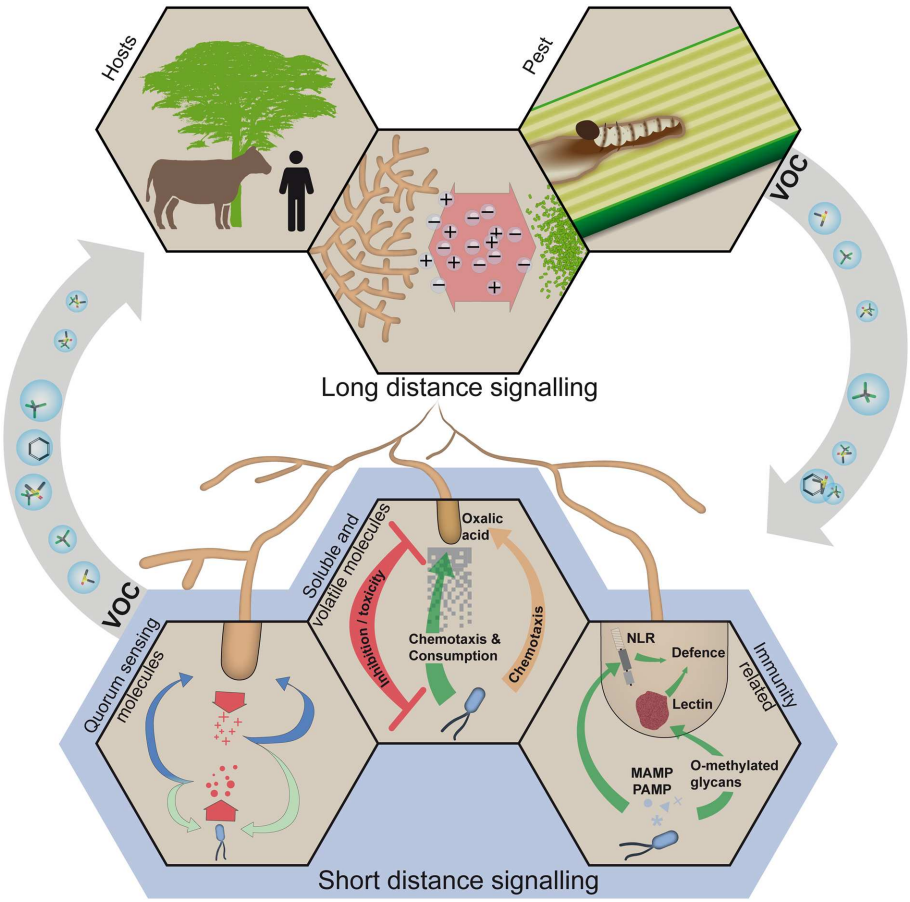

Figure 2. Short and long distance signalling in BFI. Diverse small molecules, either soluble or volatile, are perceived as a cue for the presence of the fungal/bacterial interactant during BFI. These molecules affect positively or negatively the fungal/bacterial partner, but also sometimes the hosts of BFI or additional organisms.

(Boersma *et al.* 2009; Haq *et al.* 2016). Oxalic acid would therefore serve as a sole probe of the presence of fungi in the present case.

The importance of volatile organic compounds (VOCs) in BFI signalling has long been overlooked. However, reports involving 'long-distance' signalling during BFI through VOCs originating from bacteria (Briard, Heddergott and Latgé 2016; Jones *et al.* 2017), fungi (Schmidt 2015), or synergistically from both partners (Spraker *et al.* 2014; Vahdatzadeh, Deveau and Splivallo 2015; Schmidt *et al.* 2017; Uehling *et al.* 2017) have recently accumulated. VOCs encompass a broad range of small compounds that easily diffuse through water- and gas-filled pores or tissues (reviewed in Effmert *et al.* 2012; Schmidt *et al.* 2015). In addition to their well-described fungistatic and bacteriostatic activities (Cordero *et al.* 2014; Cernava *et al.* 2015), VOCs such as terpenes or dimethyl sulphide stimulate microbial activities during BFI. For instance, the VOCs produced by *P. aeruginosa* stimulate the growth of the opportunistic pathogen *Aspergillus fumigatus*, favouring invasion of lung parenchyma by the fungus (Briard, Heddergott and Latgé 2016). Conversely, the plant-pathogenic fungus *Fusarium culmorum* produces terpenes that induce motility in the bacterium *Serratia plymuthica* (Schmidt *et al.* 2017). Interestingly, VOC production is highly influenced by nutrient availability (Hacquard 2017), and it has been proposed that microorganisms sense changes in their environments via shifts in VOC blends, adapting their behaviour accordingly (Garbeva *et al.* 2014). Intriguingly, some VOCs, such as the terpene sordorifen, are produced by both fungi and bacteria. This has led to the hypothesis that VOCs may serve as a *lingua franca* between microorganisms (Schmidt *et al.* 2017). Elucidating VOC perception mechanisms in both fungi and bacteria may answer the question whether a shared language is used by bacteria and fungi during their interactions. To date, volatile receptors have not been identified in either fungi or bacteria and the effects of VOCs on cell membrane depolarisation-based signalling during BFI remain to be measured.

Lastly, fungi may also recognise bacteria during BFI using receptors similar to plant and animal immune receptors that detect microbe-associated molecular patterns (MAMPs). Transcriptomic data have recently revealed that fungi react to similar MAMPs as plants and animals (Ipcho *et al.* 2016), and a recent survey of fungal genomes has uncovered a repertoire of putative Nod-like immune receptors or NLRs (Dyrka *et al.* 2014; Uehling, Deveau and Paoletti 2017). Some NLRs could directly recognise the presence of these MAMPs in the environment. Noteworthy is the fact that a subset of NLRs has the ability to rapidly generate new binding specificities through recombination of tandem repeat sequences (Dyrka *et al.* 2014; Uehling, Deveau and Paoletti 2017) that could favour fast adaptation to new ligands. A fungal lectin that binds bacterial lipopolysaccharide was also found to be upregulated during the interaction of the fungus *Laccaria bicolor* with different soil bacteria (Deveau *et al.* 2014; Wohlschlager *et al.* 2014). Whether these different receptors trigger immunity-like responses or are used to detect more generic BFI still needs to be determined.

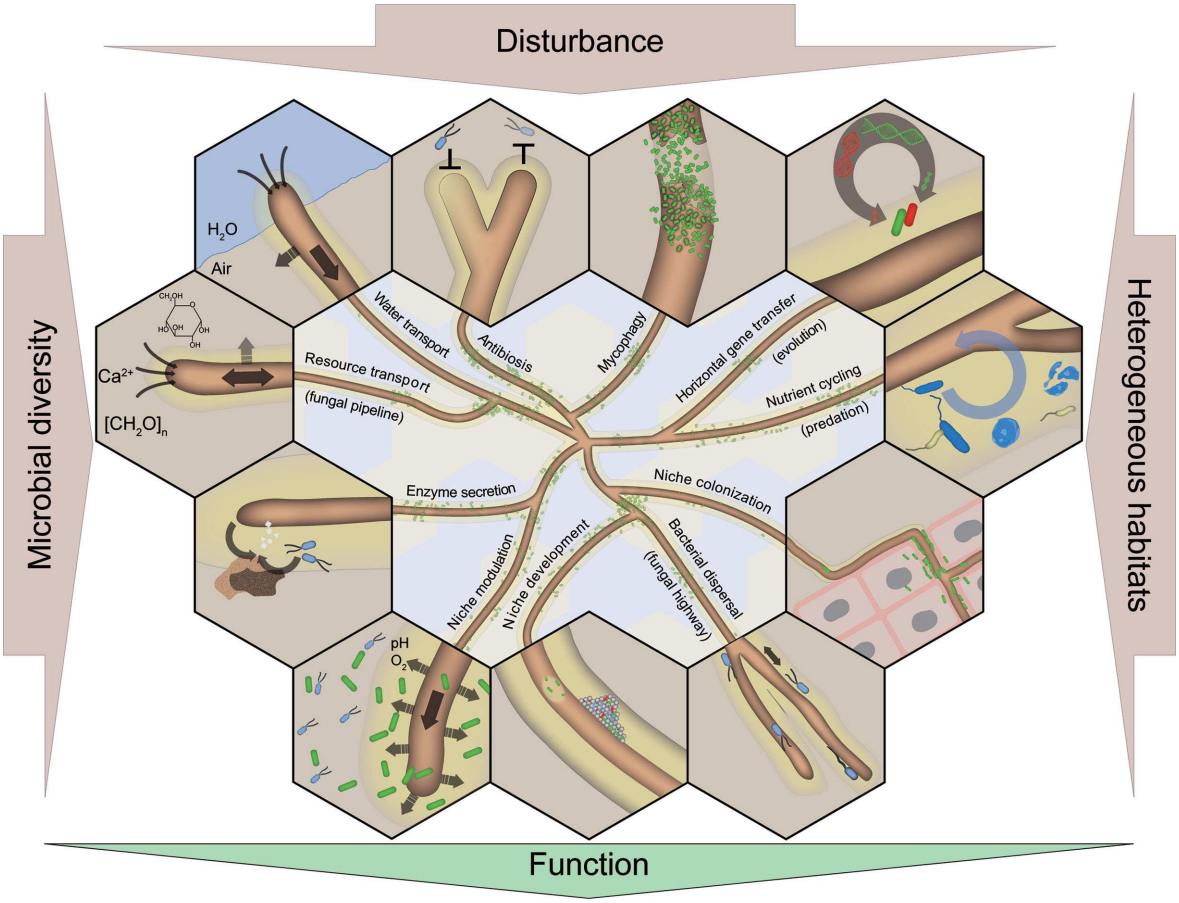

Figure 3. Microbial logistics in BFI. Fungal hyphae can efficiently colonise heterogeneous environmental habitats, create new microhabitats and thereby enable a variety of emerging ecosystem processes and services that can be beneficial or detrimental to bacteria. The mycosphere functions depend on the environment and the microorganisms involved and are highly susceptible to disturbance.

Mycelia as networks for bacterial transport

The spatial structure of the microbial habitat has been recognised to be crucial for its ecology as it drives the composition and activity of microbiomes (Andersson *et al.* 2014; Tecon and Or 2017). Spatial aspects also drive BFI (Harms, Schlosser and Wick 2011) and their better understanding will assist their use in microbial resource management. Similar to logistics of human resources and goods, microbial logistics (box 1) are essential for the functioning of microbial systems (Fig. 3). Given that mycelia vastly extend in soils (up to 10^2 m g^{-1}, 10^3 m g^{-1} and 10^4 m g^{-1} length in arable, pasture and forest soils, respectively) (Ritz and Young 2004; Joergensen and Wichern 2018), mycelia can be considered to constitute ideal transport paths and scaffolds for bacteria. The fractal structure of mycelia enables fungi to effectively exploit the three-dimensional space and to easily adapt to environmental disturbances. Fungi also cope well with heterogeneous distribution of nutrients (Boswell *et al.* 2007). A relevant feature of microbial logistics related to mycelial growth is the translocation of compounds between 'feeder' hyphae growing in optimal environments to hyphal expansion/exploration of more unfavourable areas (i.e. resource transport, Fig. 3). Likewise, fungi recycle and re-allocate their hyphal biomass from substrate-depleted regions to the benefit of exploratory colonisation of new habitats (Fricker *et al.* 2017). Hydrophobic cell wall proteins (hydrophobins) further enable hyphae to cross air-water interfaces and access heterogeneously distributed nutrients in vadose environments. Important for BFI ecology is the observation that hyphae serve as dispersal vectors for motile bacteria ('fungal highways', Kohlmeier *et al.* 2005; see https://www.youtube.com/watch?v=AnsYh6511Ic for a time lapse movie). In soil, fungal hyphae may thereby preferentially invade the larger pores that are most likely air-filled under typical field conditions (Falconer *et al.* 2012) and hence allow for bacterial dispersal at vadose conditions. This enables random and directed (e.g. chemotactic) access to new habitats and nutrients (Furuno *et al.* 2010). For instance, experiments and model simulations showed that mycelia-based bacterial dispersal stimulates contaminant biodegradation in situations where chemicals and/or bacteria are heterogeneously distributed and where the active movement of bacteria to pollutant reservoirs is limited by physical barriers (e.g. air-filled pores) (Banitz *et al.* 2011; Tecon and Or 2016; Worrich *et al.* 2016). The hyphosphere is also an ideal hotspot for the foraging of bacterial prey populations (Otto *et al.* 2016; Otto, Harms and Wick 2017) and for horizontal gene transfer, including those for antibiotic resistance, by facilitating dispersal and preferential contact of bacteria in the hyphosphere (Zhang *et al.* 2014; Berthold *et al.* 2016; Nazir *et al.* 2017). Mycelia-facilitated bacterial dispersal may likewise promote new niche colonisation (Warmink and van Elsas 2009; Martin *et al.* 2012; Simon *et al.* 2017) and contribute to bacterial food spoilage (Lee *et al.* 2014), or the co-invasion of tissues during pathogenesis (Schlecht *et al.* 2015; Jung *et al.* 2018). It may be a critical issue in the medical field, as recent studies have revealed

the existence of a variety of diverse mycobiomes related to human niches (Kalan *et al.* 2016; El-Jurdi and Ghannoum 2017).

Is it all about food acquisition? New aspects of nutrient-based BFI

It has long been known that many BFI, whether antagonistic or synergistic, rely on competition or cooperation for the acquisition of nutrients, both organic and inorganic ones (Fig. 3). Competition for nutrients has led to the development of a large chemical arsenal in both fungi and bacteria over the millions of years of interaction. Antimicrobial peptides (e.g. copsin—Essig *et al.* 2014), biosurfactants (e.g. surfactin, nunamycin—Raaijmakers *et al.* 2010; Hennessy *et al.* 2017), phenol and quinone derivatives (e.g. penicillin, atromentin—Kong, Schneper and Mathee 2010; Reen *et al.* 2016; Tauber *et al.* 2016), pyrrol nitrin (Costa *et al.* 2009), phenazines (e.g. pyocianin—Morales *et al.* 2010), QS inhibitors (Scopel *et al.* 2013; de Carvalho *et al.* 2016) to name a few, are all microbial compounds that are naturally involved in BFI (Table 1). These compounds act through a wide variety of mechanisms that include cell membrane disruption, inhibition of cell wall biosynthesis and primary metabolism, formation of reactive oxygen species against a fungus, starvation or disruption by a fungus of bacterial QS signalling (Table 1). The production of these compounds varies depending on the organisms and on environmental conditions, as exemplified by the interaction between *P. aeruginosa* and *A. fumigatus* or *C. albicans* (Lindsay and Hogan 2014; Ferreira *et al.* 2015). In response, defensive mechanisms (e.g. active efflux of antibiotics or degrading enzymes) have also been developed by target microorganisms to protect themselves (Künzler 2015). The development of protection mechanisms against toxins can also lead to cooperative behaviours between toxic fungi and bacteria as in the case of the plant pathogens *B. glumae* and *F. graminearum* (Jung *et al.* 2018). Chemical warfare in BFI can be exploited to search for new drugs and antibiotics (Reen *et al.* 2016). A number of novel compounds, e.g. glionitrin A or new members of enacyloxin family, has been uncovered through BFI analyses in the past years (Park *et al.* 2009; Ross *et al.* 2014; Tyc *et al.* 2014; Barkal *et al.* 2016). High-throughput screening of BFI has been developed to uncover cryptic or new secondary metabolites (Tyc *et al.* 2014; Navarri *et al.* 2016). Antibiotics are probably the most commonly sought-after compounds; however, other compounds such as QS inhibitors could also prove to be valuable (Scopel *et al.* 2013; de Carvalho *et al.* 2016). Given the huge unexplored metabolome space, there is great potential for the discovery of novel therapeutic approaches or methods to limit food spoilage (Debbab *et al.* 2010; Navarri *et al.* 2016). For instance, lactic acid bacteria, via the production of organic acids, hydroxyl fatty acids, hydrogen peroxide or reuterin, may restrict food spoilage (Gänzle 2015). Conversely, some compounds may be detrimental, as exemplified by the production of rhizoxin and rhizonin toxins through BFI in soybean fermentations, which can cause hepatic lesions when ingested (Rohm *et al.* 2010).

Less recognised is maybe the importance of BFI in food webs and nutrient cycling. Numbers of bacteria have the ability to degrade fungal cell walls, and bacteria are likely to have an important role in fungal biomass decomposition (Brabcová *et al.* 2016; Lladó, López-mondéjar and Baldrian 2017). Lysis of fungal cells by bacteria also stimulates biogeochemical processes such as carbon flow within the mycorrhizosphere (Ballhausen and de Boer 2016) or cellulose degradation from plant biomass as exemplified by the activities of the forest soil bacterium *Clostridium phytofermentans* (Tolonen *et al.* 2015). Plant biomass degradation often involves the action of both bacteria and fungi (Žifčáková *et al.* 2017). In the case of fungus-growing termites of the order Macrotermitinae, it has been demonstrated that the gut microbiomes of both fungal ectosymbiont (*Termytomyces*) and termite (workers) participate in plant biomass decomposition by providing a full set of complementary carbohydrate-active enzymes (Poulsen *et al.* 2014). In addition to decomposition, a large array of rhizosphere bacteria can directly consume fungal exudates, and so fungal hyphae may be an important source of nutrients in this habitat as well as in soil (Rudnick, van Veen and de Boer 2015). Some bacteria can kill and consume living fungi (i.e. mycophagy, Fig. 3). *Collimonas fungivorans* is the best-described 'mycophagous' bacterium so far, whereas other bacteria such as *S. marcescens* can also live off living fungi (Rudnick, van Veen and de Boer 2015; Ballhausen and de Boer 2016; Hover *et al.* 2016). While *Collimonas* relies on the production of secondary metabolites and chitinases to destabilise and degrade fungal cell walls (Mela *et al.* 2012), the killer activity of *S. marcescens* is independent of chitinase production and relies instead on the ability to form biofilms on the hyphae (Hover *et al.* 2016). The abilities to produce antifungal compounds are phylogenetically conserved in collimonads, suggesting the existence of co-evolution processes in this nutrient-based BFI (Ballhausen and de Boer 2016). Fungi may also be able to take advantage of their bacterial partner to improve their nutrition. Pion *et al.* (2013) demonstrated that the fungus *Morchella crassipes* is able to exploit bacterial biomass through a sophisticated mechanism coined bacterial farming, in which the fungus first feeds the bacterium *P. putida* and then harvests this self-created C source.

By contrast, mycelia of fungi (*F. oxysporum* and *Lyophillum* sp. strain Karsten) and oomycetes (*Pythium ultimum*) may enable bacterial activity by nutrient and water transfer from the hyphae to the bacterial cells exposed to oligotrophic habitats (Worrich *et al.* 2017) or favour microbial activity in dry soils (Guhr *et al.* 2015) (Fig. 3). Mycelia have also been found to mobilise entrapped polycyclic aromatic hydrocarbons (PAHs) via vesicle-bound cytoplasmic transport ('hyphal pipelines', Furuno *et al.* 2012) and to render them available to degrader bacteria (Fester *et al.* 2014; Schamfuß *et al.* 2013). Altogether, we see an emerging picture of fungi promoting ecosystem functioning in heterogeneous habitats by transporting resources from high nutrient level and water activity areas to nutrient-poor and dry areas.

BFI mediated habitat modification

Bacteria and fungi can indirectly interact by modifying their environment in ways that positively or negatively affect their partners (i.e. niche modulation, Fig. 3). pH has been frequently reported as an important factor involved in tinkering with BFI (Frey-Klett *et al.* 2011). Fungi sense and actively modulate the pH in their surroundings (Nazir *et al.* 2010; Bignell 2012; Braunsdorf, Mailänder-Sánchez and Schaller 2016). For instance, *Lyophyllum* sp. strain Karsten growing through soil was shown to raise the soil pH from levels below pH 5.0 to just above this threshold for survival of the pH sensitive *Variovorax paradoxus* and other fungal-associated bacterial strains (Nazir *et al.* 2010). Also, *C. albicans* has been shown to influence the pH of the phagolysosome to increase its chances of survival in phagocytic cells of the immune system (Vylkova and Lorenz 2014; Vylkova 2017). In addition, in combination with *Streptococcus mutans*, a cariogenic acid producing oral bacterium, *C. albicans* actively raises the environmental pH (Willems *et al.* 2016). Increasing the pH from acid

Table 1. Illustration of the diversity of antimicrobial compounds and of their targets produced by bacteria and fungi during their interactions.

Class of compounds	Compound	Producer	Target	Natural environment	Mechanisms of action	References
Antimicrobial aldehyde	Reuterin	B: *Lactobacillus reuteri*	Multiples: bacteria, fungi and more	Food	Oxidative stress	Ganzel 2015
Antimicrobial peptide	Copsin	F: *Coprinopsis cinerea*	B: Gram + and Gram −	Dung	Interference with cell wall synthesis	Essig *et al.* 2014
Antimicrobial peptide	Micasin	F: *Microsporum canis*	B: Gram + and Gram −	Human skin	Interference with protein folding	Zhu *et al.* 2012
Antimicrobial peptide	Dipeptide cis-cyclo (Leucyl-Tyrosyl)	F: *Penicillium* sp.	B: *Staphilococcus aureus*	Sponge associated	QS inhibition	Scopel *et al.* 2013
Lipopeptide	Viscosin	B: *Pseudomonas* sp.	Multiples: bacteria, fungi and more	Multiple, mainly soils and plants but also human gut, deepsea…	Membrane permeabilisation	Raaijmakers *et al.* 2010
Organo-halogenic metabolite	Pyrrol nitrin	B: Some Gram negative bacteria	F: broad spectrum	Soil	Inhibition of electron transport	Costa *et al.* 2009
Phenazines	Pyocyanine	B: *Pseudomonas aeruginosa*	F: *Candida albicans*, *Aspergillus fumigatus*	Mammals, plants	Redox and iron homeostasis	Briard, Heddergott and Latgé 2016; Morales *et al.* 2013
QS molecule	Quinolones	B: *Pseudomonas aeruginosa*	F: *Aspergillus fumigatus*, *Candida albicans*	Mammals, plants	Biofilm disruption	Reen *et al.* 2016
QS molecule	Farnesol	F: *Candida albicans*	B: *Pseudomonas aeruginosa*	Human	Interference with PQS signalling	Cugini *et al.* 2007
Siderophore	Pyoverdine	Multiples : bacteria and fungi	Multiples: bacteria, fungi and more	Multiple	Iron scavenging	Deveau *et al.* 2016
VOC	Terpenes	F: *Fusarium culmorum*	B: *Serratia* and *Collimonas*	Soil	Unknown—effect on chemotaxis	Schmidt *et al.* 2017
VOC	Blends of volatiles	B: *Collimonas* sp.	F: soil fungi	Soil	Unknown—effects on morphology and sporulation	Garbeva *et al.* 2014

towards a more neutral value directly stimulates overall bacterial growth and metabolism, as low pH commonly inhibits the growth of most bacteria.

Recent studies also identified oxygen level as an important BFI modulator, particularly for *C. albicans*—bacteria interactions. Early reports indicated that biofilms of *C. albicans* provide an anoxic environment (Bonhomme *et al.* 2011). This was later confirmed by co-culturing *C. albicans* with a variety of strict anaerobic bacterial species (Fox *et al.* 2014). In the oral cavity, rapid respiration by *C. albicans* and several other *Candida* species creates an anaerobic niche by reducing the level of dissolved oxygen (Lambooij *et al.* 2017). This favours anaerobic bacteria and antagonises aerobic ones, thereby directly influencing the composition of the microbiome (Janus, Willems and Krom 2016; Janus *et al.* 2017). Notwithstanding the afore described anaerobism, aerobic respiration is facilitated by the structure of *Candida* biofilms, and inhibition of respiration (e.g. by bacterial metabolites such as phenazines) inhibits biofilm formation by the fungus (Morales *et al.* 2013). Conversely, ethanol production by *C. albicans* stimulates phenazine production by *P. aeruginosa* and biofilm formation by the bacteria through a feedback loop, which theoretically increases virulence of both microorganisms (Chen *et al.* 2014). In light of the diversity of other fungi commonly found in the oral cavity, this oxygen-mediated effect may play an important role in more BFI in this habitat as well as many other human-associated niches.

BFI can also occur indirectly, via host behaviour modulations. For instance, bacteria and fungi induce different innate immune defences in the nematode *Caenorhabditis elegans* (Pukkila-Worley, Ausubel and Mylonakis 2011). By this means, co-infection by bacteria and fungi can alter the outcome of the disease and favour or reduce the development of the pathogens (Arvanitis and Mylonakis 2015). *Candida albicans* and *S. aureus* resulted in increased end-organ damage in murine peritonitis and higher mortality compared with single-pathogen infection. This was mediated by higher levels of circulating inflammatory cytokines (Peters and Noverr 2013). Interplays between bacteria, fungi and the innate 'immune systems' are also expected in plants (Hacquard *et al.* 2017).

Use of -omics to obtain an integrated view of BFIs

The molecular dialogue that occurs during BFI usually relies on intricate and multiple cell responses as highlighted in Table S1, Supporting Information. 'Omics' approaches are ideally suited to address such dialogues and -omics tools can be used to analyse BFI from 'simple' *in vitro* dual interactions to complex natural multispecies interactions (box 1). The past years have seen a multitude of applications of -omics to BFI (e.g. Mela *et al.* 2012; Deveau *et al.* 2014; Phelan *et al.* 2014; Benoit *et al.* 2015; Gkarmiri *et al.* 2015; Lamacchia *et al.* 2016; Li *et al.* 2017; Haq *et al.* 2017; Schmidt *et al.* 2017; Uehling *et al.* 2017; Jung *et al.* 2018). As an overriding theme, responses of partner organisms were commonly found, yet the magnitudes of the responses varied greatly, probably reflecting dependency on the types of interactions, their context, and the technology used. Interestingly, most studies demonstrated regulation of primary metabolisms including nutrient transporters, stress response, cell wall remodelling and secondary metabolite production during BFI. Noteworthy is the fact that genes/proteins with unknown functions, or showing restricted phylogenetic distribution, often represent a significant part of genes regulated in BFI. Emerging studies have been made on tripartite interactions between fungi, bacteria and a host, shedding light on the complex cross-talks occurring (Kurth *et al.* 2015; Vannini *et al.* 2016).

Complex microbial communities, being most realistic, should be examined using the combination of such analyses. The following questions emerge as relevant: 'Who is there?', 'What are they capable of?', 'Who is actively doing what?' and 'What are the factors that modify the output of the interaction?' Combining metagenomics and metaproteomics analyses, Grube deciphered the multifaceted roles of the bacteriome of the lichen *L. pulmonaria* (Grube *et al.* 2015). In this fungus-alga-bacteria symbiosis, more than 800 bacterial species contributed to the nutrient supply of the lichen, helped its resistance against fungal pathogens and abiotic stress and provided essential hormones and vitamins. Similarly, by using a combination of multi-omics approaches and soil biological techniques, Nuccio *et al.* demonstrated, for the first time, that the AMF *Glomus hoi* in *Plantago lanceolate*, significantly modified 10% of the bacterial community in decomposing litter (Nuccio *et al.* 2013). Moreover, the AMF was shown to affect the physicochemical environment in the decomposing litter by preferentially exporting N, for which it appeared to acquire N primarily in the inorganic form. This implied that the export of N from litter is one mechanism by which AMF alter the composition of the bacterial community and decomposition processes in soil.

In addition, to pinpoint functional activities within microbiomes, metaomics approaches help in determining the active players in natural conditions in microbiomes of cheese, soil or the human gut (Huttenhower *et al.* 2012; Dugat-Bony *et al.* 2015; Perazzolli *et al.* 2016; Ghodsalavi *et al.* 2017). Identifying keystone members of such microbiomes and their responses to perturbations is a current challenge of microbial ecology. To allow such studies, synthetic communities may be designed that reproduce patterns of community formation and dynamics of natural systems as well as their functional outputs. So far, much progress has been achieved in fermented food ecosystems (Wolfe and Dutton 2015). In surface-ripened cheese, key functions involved in cheese maturation process such as carbohydrate, lipid and protein metabolisms were highlighted using synthetic bacterial and fungal communities (Dugat-Bonny 2015). The consumption of lactate produced by *Lactobacillus lactis*, by the fungi *Debaryomyces hansenii* and *Geotrichum candidum* was evidenced by a high level of lactate dehydrogenase transcripts (Dugat-Bonny 2015). Moreover, the dominance of *Staphylococcus equorum* in cheese was maintained due to the presence of the fungus *Scopulariopsis* sp. *via* a molecular mechanism based on the iron utilisation pathways such as a homolog of the *S. aureus* staphyloferrin B siderophore operon pathway (Kastman *et al.* 2016).

One of the future challenges will be to take into account the spatial and temporal scales of BFI in the analyses. Even though fungi and bacteria co-colonise the same habitat, they do not have the same lifestyle in terms of colonisation area. This is particularly true for soils, in which bacterial habitats may be reduced to a soil particle of a mm^3 or specific zones in a biofilm on a root, while the hyphae of the fungus with which they locally interact forage across centimetres to meters and also interact with other plants, wood debris, microorganisms and microfauna. We here argue that there are fundamental differences in the way that bacteria and fungi respond to biotic and abiotic cues. For example, plant-associated bacterial communities show more resistance to perturbations such as in land use and pH modification than plant-associated fungal communities, while the fungal communities are more resistant to drought than bacterial communities (Uroz *et al.* 2016). Moreover, the interactive populations tend to be spatiotemporally heterogeneous, so each part

of the interacting system may be (slightly) different from each other, at different points in time during development. In addition, BFI tend to be dynamic (Young and Crawford 2004; Hennessy, Stougaard and Olsson 2017). Current methodologies used to analyse bacterial and fungal microbiomes do not allow one to take into account such complex spatiotemporal organisation. However, their use in combination with microscopy, FISH and analytic techniques such as Raman spectroscopy, Imaging Mass Spectrometry or nanoSIMS may help to overcome this limitation (Behrens *et al*. 2008; Kaltenpoth, Strupat and Svatoš 2016; Wang *et al*. 2016).

FUTURE PERSPECTIVES OF BFI RESEARCH

As highlighted in this review, important progress has been made in the understanding of BFI in model microorganisms, as well as in the description of complex microbial communities involving BFI. Within the last two decades, it has become clear that BFI are crucial to the functions in both natural and anthropogenic ecosystems, including human health. At the ecosystem scale, BFI present all types of outcomes, from positive to negative. As a result, on the one hand they represent a great potential to be harnessed, for instance in sustainable agriculture. On the other hand, the recognition of BFI with negative properties, for instance in human health, could lead to improved therapeutics. However, there is still an important gap between studies performed in laboratory conditions and the '*in vivo*' reality that impedes our ability to extrapolate generic principles of BFI at the (eco)system scale. The rapid technological advances in methodological fields related to the study of microorganisms may help in reaching such goal. The manipulation of host-associated microbiomes using either synthetic microbial communities, dilution of natural communities, CRISPR-Cas9, *Agrobacterium*-mediated and other transgenesis tools or antibiotic manipulation of microbial communities and/or germ-free hosts combined with modelling will help to identify the driving factors of BFI and of their interactions with their hosts and/or environment. Moreover, although the number of researchers integrating BFI into their studies is expanding, the field needs to become more interdisciplinary. As a result, we expect that both the methodological aspect and the interdisciplinary contribution will bring new development in the BFI research field.

Finally, BFI could also have a broader impact in science if they are used as model systems to analyse complex interactions. Indeed, apart from being an object of study, the BFI holobiont also provides an interesting and relatively simple model for the study of eukaryote–bacterial interactions. One advantage is the fact that many fungi are haploid, easy to transform (Michielse *et al*. 2005), and may be grown both in the absence or presence of bacterial partners. In this way, the BFI holobiont can become a model system for the assessment of evolutionarily conserved molecular interactions between eukaryotic cells and bacteria. A key characteristic of eukaryotic metaorganisms/holobionts is the modulated recognition of bacterial symbionts by the hosts' innate immune systems, welcoming mutualists and resisting pathogens (Artis 2008; Zamioudis and Pieterse 2012). It has long been proposed that fungi, similar to plants and animals, possess an innate immune system (Paoletti and Saupe 2009; Salvioli *et al*. 2016), and have receptors for recognising bacteria (Dyrka *et al*. 2014; Uehling, Deveau and Paoletti 2017) and indeed do so with fast transcriptomic responses (Ipcho *et al*. 2016). This opens up an exciting avenue of research into the conservation of innate immune systems across phylogenetically distant eukaryotes. BFI also serve as useful models for the study of evolutionary theory. For example, how do symbiotic bacteria–eukaryote interactions remain stable under different environmental conditions and over time (Olsson, Bonfante and Pawlowska 2017). Fungal mycelia have recently been proposed to be a driving factor of the evolution of bacterial diversity by enabling preferential contact of spatially distinct bacteria and acting as focal point for horizontal gene transfer (Zhang *et al*. 2014; Berthold *et al*. 2016). Thus, BFI may serve as models to study other eukaryotes–prokaryotes interactions, in an analogous way to how fruit flies or worms are used as models to study processes occurring in human cells (Olsson, Bonfante and Pawlowska 2017). Fungal and bacterial model systems have the advantages of being fast-growing, and easy to manipulate and track genetically. Based on these premises, BFI research should expand rapidly, not only to better understand the fundamental processes involved in BFI across research fields, and commercial and industrial settings, but also to take advantage of the fantastic properties of BFI to exploit them as model systems.

SUPPLEMENTARY DATA

Supplementary data are available at FEMSRE online.

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