

REVIEW ARTICLE

Bacterial–fungal interactions: ecology, mechanisms and challenges

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

Editor: Gerhard Braus

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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 are engaged in complex interactions that lead to critical behavioural shifts of the microorganisms ranging from mutualism to pathogenicity. 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 most 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 researches in order to catalyse a synergy within the BFI research area and to resolve outstanding questions.

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

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, they 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 degree 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, a 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



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.

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 sustainability.

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), nema-

todes (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).

Box 1. Definitions of terms and concepts

Bacterial fungiphile. Bacterial strains 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 drive 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 2016). Here, we redefine a holobiont as a “unit of bio-

logical 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.

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 fungi in the Mucoromycota (Partida-Martínez 2017; Uehling et al. 2017). 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 coevolved 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-Martínez et al. 2007; Mondo et al. 2017), growth (Shaffer et al. 2017; Uehling et al. 2017), 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 endosymbionts offer lessons in fungal endosymbiotic 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. 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 endobacteria-fungal system is the association between members of the arbuscular mycorrhizal fungal family (Gigasporaceae, Glomeromycotina) and *Candidatus Glomeribacter gigasporarum* (CaGg, 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 B12 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 B₁₂ (Grube et al. 2015).

A third fungal endosymbiont example is the endobacterium *Mycoavidus cysteinexigens*, an endosymbiont of the saprotrophic

160 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; GhodsSalavi et al. 2017). Filamentous fungi can produce differentiated tissues (e.g. mycelium, fruiting bodies, spores, mycorrhizae) that are colonised by distinguished microbiomes (Zagriadskaja 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).

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

fungus *Mortierella elongata* (Mortierellomycotina) (Uehling et al. 2017). Despite the close phylogenetic affiliation to *CaGg*, its impact on host fungal growth is strikingly different. *CaGg* 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 *CaGg* and co-evolution with the fungal host.

Interestingly, many Glomeromycotina and some Mucoromycota, such as *Endogone*, can host bacterial endosymbionts belonging to the Mollicutes (Naumann, Schüssler and Bonfante 2010; Desirò et al. 2014; Desirò et al. 2015); some have been identified as novel types named ‘Candidatus *Moeniiplasma glomeromycotarum*’ (*CaMg*) (Naito et al. 2017). The effect of *CaMg* on the fungal host is still unknown, although molecular evolution analyses indicate that they could be fungal parasites in some cases (Toomer et al. 2015). Remarkably, genome sequencing of selected *CaMg* revealed evidence of horizontal gene transfer events, in particular of fungal genes to the endosymbiont involved in post-translational modification (Naito, Morton and Pawlowska 2015; Torres-Cortés et al. 2015). Ongoing studies now aim at determining the function of *CaMg*; 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), possibly via type III secretion systems (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 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. Though shotgun sequencing of such samples may be suggestive of fungal endosymbiont symbioses,

the presence and taxonomic identity of endofungal bacteria should still be demonstrated with 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, 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 (Dharmagay, 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 disease, 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 INTERACTIONS

A suite of molecular mechanisms may underlie BFI in different systems relying on a combination of physical and chemi-

cal 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 peculiar 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 since 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; Sztajner 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 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; Sztajner 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). But they 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

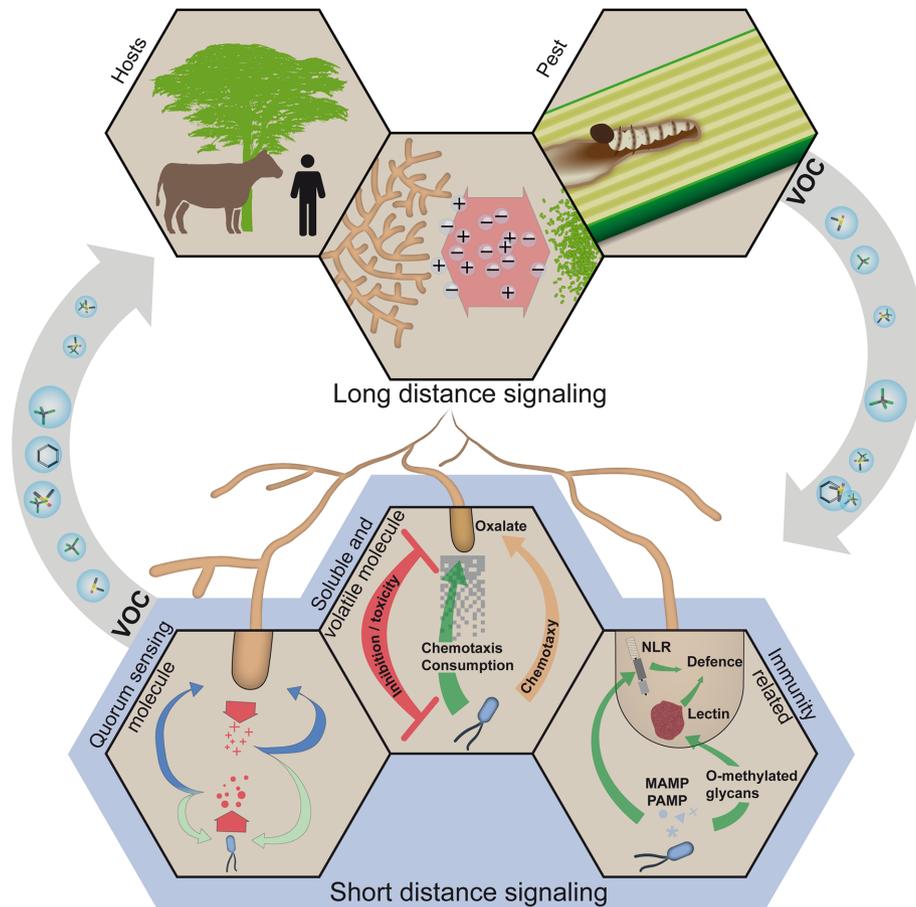


Figure 2. Short and long distance signalling in BFI. Diverse small molecules, either soluble or volatile, are perceived as a cue for the presence of the fungal/bacterial interactant during BFI. These molecules affect positively or negatively the fungal/bacterial partner but also sometimes the hosts of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

pothesis 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.

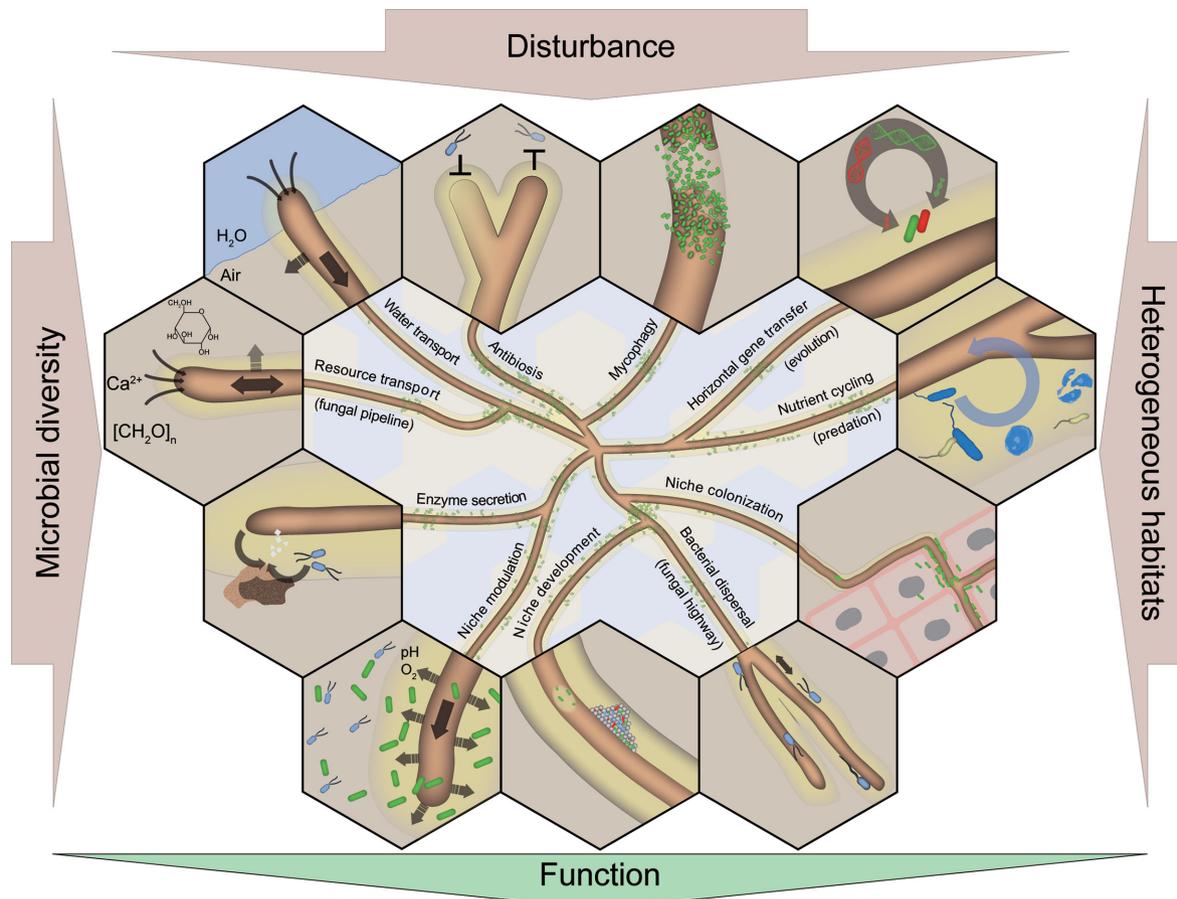


Figure 3. Microbial logistics in BFI. Fungal hyphae can efficiently colonise heterogeneous environmental habitats, creating new microhabitats and thereby enabling a variety of emerging ecosystem processes and services that can be beneficial or detrimental to bacteria. The mycosphere functions depend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

Mycelia as networks for bacterial transport

The spatial structure of the habitat has been recognised to be crucial in microbial ecology as it drives the composition and activity of microbiomes (Andersson et al. 2014; Tecon and Or 2017). Clearly, BFI are also shaped by spatial aspects (Harms, Schlosser and Wick 2011) and further enhanced knowledge will assist their use in microbial resource management. Similar to logistics of management of human resources and goods, microbial logistics (box 1) are essential for the functioning of microbial systems (Fig. 3). In the light of the extent of mycelial networks 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), these can be considered to constitute ideal transport paths and scaffolds for bacteria. The fractal mycelial structure enables fungi to effectively exploit the three-dimensional space, easily adapting 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 hy-

phae to cross air 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=AnsYh6511c> 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 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; Worrlich 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 promote new niche colonisation (Warmink and van Elsas 2009; Martin et al. 2012; Simon et al. 2017) and participate 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. cospin—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. pyocyanin—Morales et al. 2010), QS inhibitors (Scopel et al. 2013; de Carvalho et al. 2016) to name a few, are all microbial compounds 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 toxin 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). Number of novel compounds, e.g. glionitrin A or new members of enacyloxin family, have 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; Navari 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; Navari et al. 2016). For instance, lactic acid bacteria, via the production of organic acids, hydroxyl fatty acids, hydrogen peroxide or reuterin, may protect against 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 bacterial biomass decomposition (Brabcová et al. 2016; Lladó, López-mondéjar and Baldrian 2017). Fungal lysis by bacteria also stimulate 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 both fungal ectosymbiont (*Termytomyces*) and termite (workers) gut microbiomes participate in plant biomass decomposition by providing a full set 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 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 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 *Lyophyllum* 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). For instance, 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

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: <i>Lactobacillus reuteri</i>	Multiples: bacteria, fungi and more	Food	Oxidative stress	Ganzel 2015
Antimicrobial peptide	Copsin	F: <i>Coprinopsis cinerea</i>	B: Gram + and Gram -	Dung	Interference with cell wall synthesis	Essig et al. 2014
Antimicrobial peptide	Micasin	F: <i>Microsporium canis</i>	B: Gram + and Gram -	Human skin	Interference with protein folding	Zhu et al. 2012
Antimicrobial peptide	Dipeptide	F: <i>Penicillium</i> sp.	B: <i>Staphylococcus aureus</i>	Sponge associated	QS inhibition	Scopel et al. 2013
Lipopeptide	cis-cyclo(Leucyl-Tyrosyl) Viscosin	B: <i>Pseudomonas</i> 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: <i>Pseudomonas aeruginosa</i>	F: <i>Candida albicans</i> , <i>Aspergillus fumigatus</i>	Mammals, plants	Redox and iron homeostasis	Briard, Heddergott and Latgé 2016; Morales et al. 2013
QS molecule	Quinolones	B: <i>Pseudomonas aeruginosa</i>	F: <i>Aspergillus fumigatus</i> , <i>Candida albicans</i>	Mammals, plants	Biofilm disruption	Reen et al. 2016
QS molecule	Farnesol	F: <i>Candida albicans</i>	B: <i>Pseudomonas aeruginosa</i>	Human	Interference with PQS signaling	Cugini 2009
Siderophore	Pyoverdine	Multiples : bacteria and fungi	Multiples: bacteria, fungi and more	Multiple	Iron scavenging	Deveau et al. 2016
VOC	Terpenes	F: <i>Fusarium culmorum</i>	B: <i>Serratia</i> and <i>Collimonas</i>	Soil	Unknown—effect on chemotaxis	Schmidt et al. 2017
VOC	Blends of volatiles	B: <i>Collimonas</i> sp.	F: soil fungi	Soil	Unknown—effects on morphology and sporulation	Garbera et al. 2014

pH from acid 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 (Lambooi 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 theafore 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 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 mean, 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 2014; Benoit 2015; Gkarmiri et al. 2015; Lamachia 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; Vanini 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 demonstrated, for the first time, that the AMF *Glomus hoi* in *Plantago lanceolata*, 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; Perazzoli et al. 2016; Ghodsalavi et al. 2017). Identifying keystone members of such microbiomes and their response 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, good progress has been achieved in fermented food ecosystems (Wolfe and Dutton 2015). In surface-ripened cheese, BFI regarding 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). Thus, 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 of such approach will be to take into account the spatial and temporal scales of BFI in their analysis. 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 mm³ 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 and resilience than fungi to environmental perturbations such change in land use or pH modifications while fungi better resist than bacteria to drought (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, BFIs present all type 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, agrobacterial 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 evolutionary 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, like plants and animals, possess an innate immune system (Paoletti and Saupe 2009; Salvioli et al. 2016), have receptor candidates 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 phylo-

genetically 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 to grow, 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](https://femsre.onlinelibrary.wiley.com/doi/10.1111/femsre.12444) online.

ACKNOWLEDGEMENTS

This cooperative work was initiated following the workshop on Bacterial–Fungal Interactions at the 2016 European Conference on Fungal Genetics (ECFG) and the authors would like to acknowledge the ECFG to have supported for the organisation of such networking workshop. We thank Guillaume Cailleau for his critical help in figure designing. We also thank the anonymous reviewers for their comments and suggestions which greatly increased the quality of this manuscript.

FUNDING

AD and SM are supported by the French National Research Agency through the Laboratory of Excellence ARBRE (ANR-12-LABXARBRE-01) and the INRA Metaprogram MEM. BPK is supported by a grant from the University of Amsterdam for research into the focal point 'Oral Infections and Inflammation'. GB acknowledges MSU and AgBioResearch for research support. The work of LYW was co-funded by the Deutsche Forschungsgemeinschaft (DFG) CRC 1076 'AquaDiva' and the Helmholtz Centre for Environmental Research. LM, JL and JU were supported by the US Department of Energy, Office of Science, Biological and Environmental Research as part of the Plant-Microbe Interfaces Scientific Focus Area (<http://pmi.ornl.gov>). Oak Ridge National Laboratory is managed by UT-Battelle, LLC, for the US Department of Energy under contract DE-AC05-00OR22725. SB and PJ supported by several grants from the Swiss National Science Foundation (SNSF) and the Commission for Technology and Innovation (CTI) of the Swiss confederation. VH was supported by the Swiss National Science Foundation through Grant FN CR3212-149853/1. VB was supported by the European Union and the State of Hungary, co-financed by the European Social Fund in the framework of TÁMOP 4.2.4. A/1-11-1-2012-0001 'National Excellence Program' (A1-MZPD-12-0166). SO acknowledge FAFU for research support. PB was supported by the University of Torino (60% Project). SH is supported by the Max Planck Society.

Conflict of interest. None declared.

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GRAPHICAL ABSTRACT

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

