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Bacterial - Fungal Interactions: ecology, mechanisms and challenges

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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 regards 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.

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 2010; Scherlach 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 (Figure 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 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 multi-partner interactions can occur within a single environment - such as in the oral plaque (Janus 2016), in soil (Warmink 2009), in a single food product (Kastman 2016), or across multiple environments. Opportunistic microorganisms such as the aforementioned P. aeruginosa colonize 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 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 (Figure 1).
Within the past decade, a range of multidisciplinary studies on diverse BFI, that 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 (2011) and Scherlach (2013). Such generalist patterns mirrors the remarkable similarities shared between plants and animals recently documented in microbiota assisted host nutrition (Hacquard 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.

1. BFI within complex networks of interactions: from fungal microbiomes to meta-organisms 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 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 2014; Lindsay and Hogan 2014; Urich 2014; Douterelo 2016; de Menezes 2017) to networks involving higher organisms, in which BFI occur within the microbiomes of hosts such as lichens (Grube 2015), corals (Moree 2013), nematodes (Wang 2014), insects (Aylward 2014), batrachians (Longo and Zamudio 2017) or mammals (Hacquard 2015; Hoyt 2015). In this regard, the interacting microorganisms together may be conceptually regarded as one metaorganism (Olsson 2017, see box 1).

The fungal microbiome
The hyphosphere (box 1) provides microhabitats that are colonized by specific bacterial communities (Frey-Klett 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 2015; Wolfe and Dutton 2015; Schulz-Bohm 2016; Ghodsalavi 2017). Filamentous fungi can produce differentiated tissues (e.g. mycelium, fruiting bodies, spores, mycorrhizae) that are colonized by distinguished microbiomes (Zagriadskaia 2013; Deveau 2016; El-Jurdi and Ghannoum 2017). While some bacteria, such as Burkholderia spp., can colonize a large set of fungal species given their abilities to utilize fungal-derived metabolites and overcome fungal defence mechanisms (Haq 2014; Stopnisek 2016; Jung 2018), others may have a more specific and intimate relationship with their fungal hosts (Warmink 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 2015; Schulz-Bohm 2016; Mondo 2017; Uehling 2017a).
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 a review, see Wolfe and Dutton 2015), as well as cultivation of edible mushrooms (Murat 2014; Bánfi 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 2016; Shaffer 2016), symbiotic, pathogenic and endophytic Basidiomycetes (Bertaux 2003; Ruiz-Herrera 2015; Glaeser 2016) as well as saprotrophic fungi in the Mucoromycota (Partida-Martínez 2017; Uehling 2017a). 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 2017a). These associations appear to be specific, and have presumably tightly coevolved over millions of years (Mondo 2012; Desirò 2015; Uehling 2017a). This has resulted in host dependency and significant genome reductions for the bacterial endosymbionts (Ghignone 2012; Uehling 2017a). Endobacteria can have profound effects on fungal host biology, including aspects of host reproduction (Partida-Martinez 2007; Mondo 2017), growth (Shaffer 2017; Uehling 2017a), energy dynamics (Salvioli 2016; Vannini et 2016), primary metabolism (Lastovetsky 2016; Salvioli 2016; Vannini 2016; Li 2017; Uehling 2017a), and secondary metabolism (Rohm 2010; Hoffman 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 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 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 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 2016). Recent work discovered a new aspect of the endobacterial biology, in that a toxin-antitoxin system was active (Salvioli 2017), as well as the whole operon for vitamin B12 production (Ghignone 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 hypothesized to support photosynthesis by provision of vitamin B12 (Grube 2015).

A third fungal endosymbiont example is the endobacterium Mycoavidus cysteinexigens, an endosymbiont of the saprotrophic fungus Mortierella elongata (Mortierellomycotina)(Uehling 2017a). 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 2017a) suggesting that

these later endobacteria utilize 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 2010; Desirò 2014; Desirò 2015); some have been identified as novel types named ―Candidatus Moeniiplasma glomeromycotarum‖ (CaMg) (Naito 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 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 2015; Torres-Cortés 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 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 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 2016).
The mechanisms by which endofungal bacteria colonize their hosts have been deciphered for only a few examples. P. rhizoxinica actively secretes chitinolytic enzymes by means of the type II secretion system, to penetrate the hyphae of the R. microsporus host (Moebius 2014). In contrast, Ralstonia solanacearum requires the production of the lipopeptide ralsomycin to invade the chlamydospores of its fungal hosts (Spraker 2016). Once inside the mycelium, some bacteria, much like mitochondria, are able to move through dolipore septa (Bertaux 2005). Some can also be vertically transmitted between generations through fungal spores (Spraker 2016), possibly via type III secretion systems (Lackner 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 2013; Vannini 2016; Guo 2017) or detrimental (Lackner and Hertweck 2011) associations, giving rise to multi-level inter-kingdom 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 (TEM) and fluorescence in situ hybridization (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 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 2016). This ubiquitous association, together with co-cultivation experiments under laboratory conditions, suggest that specific soil bacteria have evolved strategies to utilize fungal-secreted metabolites and overcome fungal defence mechanisms (Stopnisek 2016). Interactions involving hub microorganisms or keystone species (box

1) can be then further investigated at the molecular level. Agler and coworkers thus identified the yeast Dioszegia as a fungal hub of the phyllosphere microbiome of Arabidopsis thaliana, as well as its bacterial interactants (Agler 2016). This methodology has already identified BF networks and the drivers that govern community assembly in leaf litter (Purahong 2016), soils (de Menezes 2014; Ma 2016; Stopnisek 2016), floral nectar (Álvarez-Pérez and Herrera 2013), plants (Bell 2014; Agler 2016) and human microbiomes (Mukherjee 2014; Trosvik and de Muinck 2015). All these studies revealed non-random associations between fungi and bacteria and an overrepresentation 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 colonization 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 2014; Ma 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 2016; Purahong 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 2016).

An ecological balance within the microbiome and between the microbiome and the host (host-microbiota homeostasis) has been hypothesized to be fundamental to maintaining the health of both animal and plant hosts (Krom and Oskam 2014; Hacquard 2017a). 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 immuno-compromised patients, as well as in (recurrent) bowel disease, or related to the use of invasive medical devices (Dhamgaye 2016; Förster 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. Expósito 2017; Santhanam 2015; Ritpitakphong 2016). 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 2015; Koskella 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 2015; Mousa 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 2015; Poudel 2016), or treating dysbiosis in animals and plants using microbiome-based strategies (Fraune 2015; Santhanam 2015; Adam 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 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 2014; Dugat-Bony 2015; Liu 2015), 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 recognized as important members of Earth‘s biosphere in terms of their contribution to ecosystem functioning (Moissl-Eichinger 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 2016), the mycorrhizosphere (Bomberg and Timonen 2009), rhizosphere (Thion 2016), soil (Ma 2016), rumen (Kumar 2015) and human gut (Hoffmann 2013). However, to date, only few studies have investigated the bacterial-archaeal (Raymann 2017), archaeal-fungal (Hoffmann 2013; Kumar 2015) and fungal-bacterial-archaeal (Ma 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 2013).

2. Mechanisms of interactions

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 (2011) and illustrated in Suppl. Table 1. Such mechanisms were conceptually divided into four classes, i.e. (1) antibiosis involving metabolite exchange, (2) signalling and chemotaxis involving metabolite sensing and conversion, (3) physicochemical changes following adhesion and (4) 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 plays 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 recognize 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 2011; Sztajer 2014; Gkarmiri 2015; Haq 2017; Tomada2017). Several cues may be used by the microorganisms for mutual detection, and most are based on small signalling molecules (Scherlach and Hertweck 2017) (Figure 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 2016). Furthermore, both bacterial and fungal QS molecules were shown to play significant roles in cross-kingdom signalling (Cugini 2007; Stanley 2014; Sztajer 2014; Dixon and Hall 2015). Indeed, certain bacteria react to fungal QS molecules (e.g. farnesol, tyrosol, phenylethanol, tryptophol; Wongsuk 2016), and, conversely, fungi may react to bacterium-secreted compounds (e.g. quinolone signals, homoserine lactones; Dixon and Hall 2015; Fourie 2016). Such inter-kingdom 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 2014; Dixon and Hall 2015; Fourie 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 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 2015; Haq 2016a). This is in contrast to most other compounds (e.g. glycerol) that are later used as a source of nutrients by fungal-associated bacteria (Boersma 2009; Haq 2016b). 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 2016; Jones 2017), fungi (Schmidt 2015), or synergistically from both partners (Spraker 2014; Vahdatzadeh 2015; Schmidt 2017, Uehling 2017a) 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 2012; Schmidt 2015). In addition to their well-described fungistatic and bacteriostatic activities (Cordero 2014; Cernava 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 2016). Conversely, the plant-pathogenic fungus Fusarium culmorum produces terpenes that induce motility in the bacterium Serratia plymuthica (Schmidt 2017). Interestingly, VOC production is highly influenced by nutrient availability (Hacquard 2017b) and it has been proposed that microorganisms sense changes in their environments via shifts in VOC blends, adapting their behaviour accordingly (Garbeva 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 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 depolarization-based signalling during BFI remain to be measured.

Lastly, fungi may also recognize 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 2016), and a recent survey of fungal genomes has uncovered a repertoire of putative Nod-like immune receptors or NLRs (Dyrka 2014; Uehling 2017b). Some NLRs could directly recognize 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 2014; Uehling 2017b) 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 2014; Wohlschlager 2014). Whether these different receptors trigger immunity-like responses or are used to detect more generic BFI still needs to be determined.

Mycelia as networks for bacterial transport

The spatial structure of the habitat has been recognized to be crucial in microbial ecology as it drives the composition and activity of microbiomes (Andersson 2014; Tecon and Or 2017). Clearly, BFI are also shaped by spatial aspects (Harms 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 (Figure 3). In the light of the extent of mycelial networks in soils (up to 102 m g-1, 103 m g-1 and 104 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 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, Figure 3). Likewise, fungi recycle and re-allocate their hyphal biomass from substrate-depleted regions to the benefit of exploratory colonization of new habitats (Fricker 2017). Hydrophobic cell wall proteins (hydrophobins) further enable hyphae 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 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 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 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 2011; Tecon and Or 2016; Worrich 2016). The hyphosphere is also an ideal hotspot for the foraging of bacterial prey populations (Otto 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 2014; Berthold 2016; Nazir 2017). Mycelia-facilitated bacterial dispersal may promote new niche colonization (Warmink and van Elsas 2009; Martin 2012; Simon 2017) and participate to bacterial food spoilage (Lee 2014), or the co-invasion of tissues during pathogenesis (Schlecht 2015; Jung 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 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 (Figure 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 2014), biosurfactants (e.g. surfactin, nunamycin - Raaijmakers 2010; Hennessy 2017a), phenol and quinone derivatives (e.g. penicillin, atromentin - Kong 2010; Reen 2016; Tauber 2016), pyrrol nitrin (Costa 2009), phenazines (e.g. pyocianin - Morales 2010), QS inhibitors (Scopel 2013; de Carvalho 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 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 Burkholderia glumae and Fusarium graminearum (Jung 2018). Chemical warfare in BFI can be exploited to search for new drugs and antibiotics (Reen 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 2009; Ross 2014; Tyc 2014; Barkal 2016). High-throughput screening of BFI has been developed to uncover cryptic or new secondary metabolites (Tyc 2014; Navarri 2016). Antibiotics are probably the most commonly sought-after compounds, however other compounds such as QS inhibitors could also prove to be valuable (Scopel 2013; de Carvalho 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 2010; Navarri 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, that can cause hepatic lesions when ingested (Rohm 2010).

Less recognized 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 2016; Lladó 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 2015). Plant biomass degradation often involves the action of both bacteria and fungi (Žifčáková 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 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, 2015). Some bacteria can kill and consume living fungi (i.e mycophagy, Figure 3). Collimonas fungivorans is the best-described ‗mycophagous' bacterium so far, whereas other bacteria such as Serratia marcescens can also live off living fungi (Rudnick 2015, Ballhausen 2016, Hover 2016). While Collimonas relies on the production of secondary metabolites and chitinases to destabilize and degrade fungal cell walls (Mela 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 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 (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 Pseudomonas putida and then harvests this self-created C source.

By contrast mycelia of fungi (Fusarium 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 2017) or favour microbial activity in dry soils (Guhr 2015)(Figure 3). Mycelia have also been found to mobilize entrapped polycyclic aromatic hydrocarbons (PAHs) via vesicle-bound cytoplasmic transport (‗hyphal pipelines', Furuno 2012) and to render them available to degrader bacteria (Fester 2014, Schamfuß 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, Figure 3). For instance, pH has been frequently reported as an important factor involved in tinkering with BFI (Frey-Klett 2011). Fungi sense and actively modulate the pH in their surroundings (Nazir 2010; Bignell 2012; Braunsdorf 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 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 2016). Increasing the 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 2011). This was later confirmed by co-culturing C. albicans with a variety of strict anaerobic bacterial species (Fox 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 2017). This favours anaerobic bacteria and antagonises aerobic ones, thereby directly influencing the composition of the microbiome (Janus 2016; Janus 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 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 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 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). C. 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 2017a).

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 Supplemental Table 1. —Omics‖ approaches are ideally suited to address such dialogues and -omics tools can be used to analyze 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 2012, Deveau 2014, Phelan 2014, Benoit 2015, Gkarmiri 2015, Lamachia 2016, Li 2017, Haq 2017, Schmidt 2017, Uehling 2017a, Jung 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 2015; Vannini 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 Lobaria pulmonaria (Grube 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 lanceolate, significantly modified 10% of the bacterial community in decomposing litter (Nuccio 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, meta-omics approaches help in determining the active players in natural conditions in microbiomes of cheese, soil or the human gut (Huttenhower 2012; Dugat-Bony 2015; Perazzolli 2016; Ghodsalavi 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 utilization pathways such as a homolog of the S. aureus staphyloferrin B siderophore operon pathway (Kastman 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-colonize the same habitat, they do not have the same lifestyle in terms of colonization 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 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 2017b). Current methodologies used to analyse bacterial and fungal microbiomes do not allow one to take into account such complex spatiotemporal organization. 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 2008; Kaltenpoth 2016; Wang 2016).

3. 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 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 meta-organisms/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 2016), have receptor candidates for recognizing bacteria (Dyrka 2014; Uehling 2017b) and indeed do so with fast transcriptomic responses (Ipcho 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 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 2014; Berthold 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 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.

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