Fungal—bacterial interactions: a mixed bag of mingling microbes

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Fungi and bacteria co-inhabit a wide variety of environments, from soils and food products to plants and mammals. Interactions between bacteria and fungi can have dramatic effects on the survival, colonization and pathogenesis of these organisms. There are instances where bacteria provide fungi with compounds that enhance the production of fungal virulence determinants. Other bacteria produce factors that are likely to inhibit pathogenesis by repressing fungal filamentation. Furthermore, mixed bacterial–fungal biofilms can have properties that are distinct from their single-species counterparts. Clinical studies, in combination with *in vitro* model systems, are necessary to understand how bacterial–fungal interactions impact human health.

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Introduction

Fungi are capable of colonizing almost every niche within the human body. Effects of this fungal colonization can range from superficial infections of the skin and toenails to disseminated diseases that can be life-threatening. In many cases, host-associated fungi are found within microbial communities comprised of an array of different bacterial and fungal species. We are only just beginning to develop tools that will enable us to measure the extensive microbial diversity that inhabits mammals [1,2], and progress is being made in identifying and quantifying the numerous fungi present, the populations and diversity of which are only now being examined [3]. The mechanisms of interaction between fungi and bacteria are undoubtedly diverse. A summary of mechanisms by which bacteria interact with fungi is shown in Figure 1. In this review, we focus on direct interactions between microbes and do not cover indirect bacterial–fungal interactions mediated through the host. The goals of this review are to summarize the recent clinical findings on the importance of bacterial–fungal interactions on human health and disease, to examine the progress that has been made in understanding these interactions using *in vitro* model systems, and to briefly explore advances in research on bacterial–fungal interactions in non-medical fields such as plant and food microbiology.

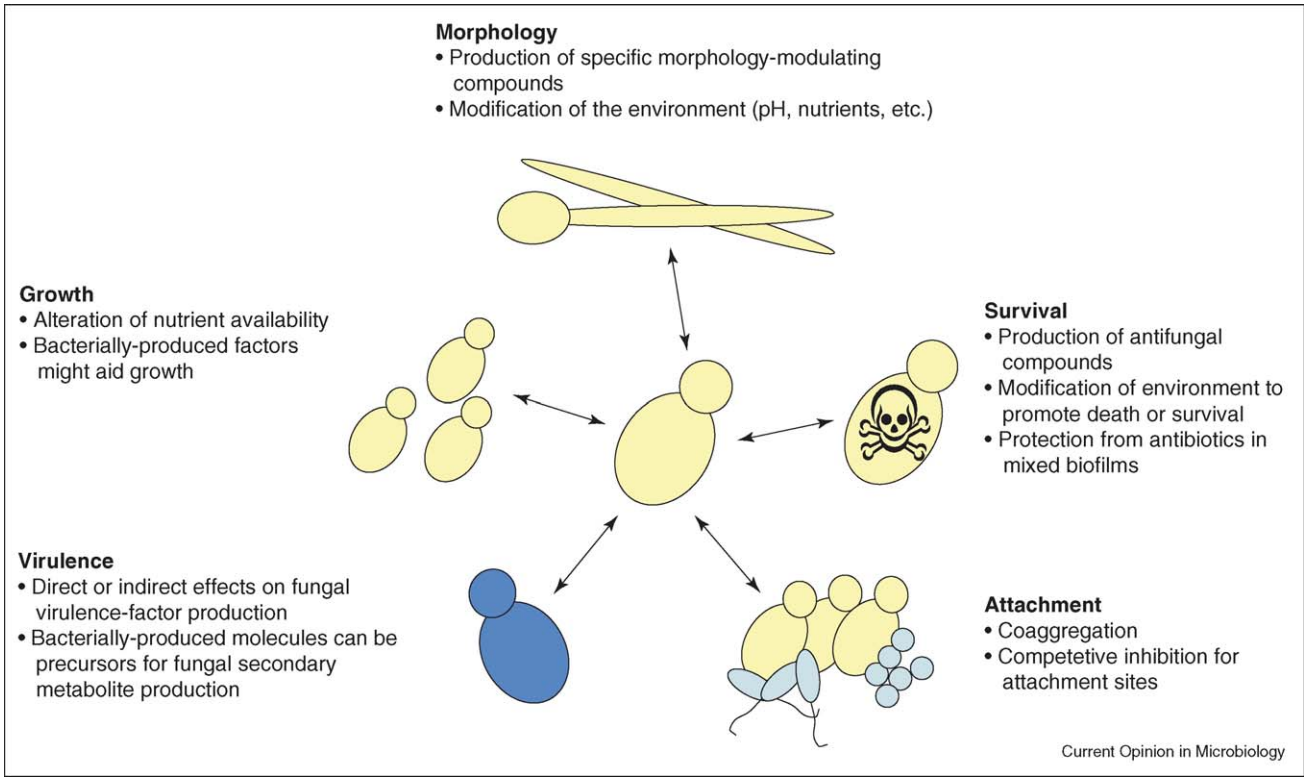
Candida-bacterial interactions

Because *Candida albicans* is one of the most problematic human fungal pathogens, the majority of research on bacterial–fungal interactions has focused on this organism. *C. albicans* is a common member of the dermal, oral and intestinal microflora of humans, as well as being an opportunistic pathogen, capable of causing a wide range of infections. It is important to consider bacterial–*Candida* interactions in the study of fungal virulence for a number of reasons. First, it has been shown that in many cases, *C. albicans* strains responsible for infections probably originate from the patient's own microflora [4]. Aspects of the host's microbial community might normally protect against fungal proliferation or might play an important role in the preparation of the fungus for its role in the infection. Second, mixed bacterial–fungal infections might have properties that are distinct from single-species infections. Lastly, the study of *C. albicans* interactions with bacteria might provide insight into new strategies that can be exploited for the control of candidiasis. Below, we describe clinical research on the role of *Candida*–bacteria interactions in disease, along with the *in vitro* studies designed to uncover the molecular mechanisms that govern *in vivo* observations.

Candida–bacteria interactions within biofilms

Candida causes a large number of infections related to implanted medical devices [5]. Evidence suggests that these implant-associated infections are a result of *Candida* biofilm formation [6] and, in many cases, mixed microbial biofilms are detected. While examining denture stomatitis, Baena-Monroy *et al.* [7] identified a significant association between *C. albicans* and *Staphylococcus aureus*. Of the 50 patients with atrophic denture stomatitis, 39 had *C. albicans* and *S. aureus* co-colonization. These co-species communities, probably existing as a mixed biofilm, are difficult to treat with antibiotics and antifungals. Previous research on implant-related infections also showed the frequent incidence of formation of mixed-species biofilms on catheters [5,8–10]. Mixed biofilms might be more resistant as a result of more complex matrix composition, and it has been proposed that antibiotic resistance profiles change in mixed infections.

Figure 1



Bacterial effects on fungal growth, survival and virulence. The different ways that bacteria can affect fungi are divided into five categories, although these interactions are not necessarily mutually exclusive. The bidirectional arrows indicate that, in different circumstances, bacteria might either enhance or attenuate the fungal properties illustrated. These interactions are highly dependent on many factors, including the bacterial and fungal species involved, the surrounding microbial community and the host environment.

O'May *et al.* [11•] designed a complex in vitro fermenter system to replicate the biofilms that form within gastric feeding tubes in an effort to model the efficacy of potential therapies. This chemostat fermenter was inoculated with the 11 most common strains found in clinical gastric feeding tube samples, including *C. famata*. In this model, mixed-species biofilms formed on the chemostat tubing, with micro-colonies typically composed of both yeast and bacterial cells. *Candida* pseudohyphae were observed bridging adjacent colonies, and perhaps were the cause of bacterial killing observed in the regions directly adjacent to these pseudohyphae. Acid suppression therapy was found to alter community structure in favor of *Candida*. The resultant biofilm community, composed of *Candida* cells and an unidentified assortment of the initial bacterial species, was able to persist and grow at a pH less than three, supporting a role for biofilms in protecting the microbial community from environmental pressures and shedding light on the efficacy of current treatments. With this complex model system in place, we can study the physical and chemical interactions between species by altering the species-composition of the inoculum. El-Azizi *et al.* [12] examined the physical interactions between *C. albicans* and a number of known biofilm-forming pathogenic bacteria. This study implicates surface polysaccharides as playing an important role in the colonization of bacterial biofilms by *C. albicans* and in the colonization of *C. albicans* biofilms by bacteria. Specifically, glycocalyx-producing bacteria were able to better adhere to *C. albicans* biofilms; conversely, the fungus could not attach as easily to preformed biofilms of glycocalyx-producing bacteria.

Candida–bacteria interactions in association with host tissues

Several studies indicate that interactions between bacteria and *Candida* species might play a role in the colonization of host niches. Burn victims are susceptible to a wide range of opportunistic pathogens as a result of the breakdown of the skin barrier and alteration of immune function in the region of the burn wound. Fungi are often present in conjunction with bacteria, and a very common burn-associated fungus is *C. albicans*. In a study of 300 burn patients, Gupta *et al.* [13] determined that *Candida* species co-infected burn wounds with bacteria in 59% of cases. However, when *Pseudomonas aeruginosa* was present, fungal colonization was significantly inhibited. This result supports *in vitro* data that *P. aeruginosa* is able to

inhibit the growth of, and even kill *C. albicans* [14–16]. Furthermore, the 3-oxo-C12-acyl homoserine lactone-signaling molecule produced by *P. aeruginosa* inhibits *C. albicans* hyphal formation [17]. However, whereas these studies provide a possible explanation for the *in vivo* inhibition of *Candida* species in *P. aeruginosa*-infected burn wounds, it is also plausible that *P. aeruginosa* specifically alters the host-response or host-environment, thus inhibiting *C. albicans* co-infection.

Mixed bacterial–fungal populations are commonly found in the oral environment and have been recently studied in the context of root canal infections [18] and in root caries [19]. Such oral *Candida*–bacteria interactions might have clinical relevance in terms of initial colonization, infection, and treatment of these poly-microbial infections. In efforts to study the physical interactions between the bacteria and *C. albicans*, a pair-wise analysis was performed using members of the microflora found associated with root caries [19]. None of the 21 species that preferentially infect tooth root caries were able to co-aggregate with *C. albicans*, unlike many members of the oral microflora species previously tested [20]. Co-aggregation might play a number of roles in controlling infection by resulting in changes in the interacting species or changes to the host environment that controls the balance between innocuous residence and rampant invasion; this type of control might be absent in root caries.

Controlling fungal infections through the use of probiotic organisms

Numerous studies have reported that the use of broad-spectrum anti-bacterial antibiotics predisposes an individual to *C. albicans* infections, suggesting that host-associated bacteria play a role in controlling *C. albicans* populations. On the basis of data that suggests that normal host-associated bacteria can protect against fungal overgrowth, there is much interest in the use of probiotic organisms as a cost-effective, low-risk method for protecting against infectious agents such as fungi. Several recent reviews summarize the probiotics field [21,22]. Lactobacilli have been the most widely used probiotic organisms and success in their use as protection from fungal infection is encouraging [23,24]. Noverr *et al.* [25•] examined the effects of lactic acid bacteria on morphogenesis of *C. albicans*. Culture supernatants from select lactic acid bacteria (LAB), especially *Lactobacillus rhamnosus* GG, were able to inhibit the transition of *C. albicans* from yeast to hyphae, which is consistent with previous reports [26]. This effect was mimicked by the presence of as little as 25 mM butyric acid, a concentration well within the physiologic range observed in the colon. This short chain fatty acid is a major metabolic by-product of many LAB species. In the host, especially in the intestine and female reproductive tract where LAB are plentiful, the butyric acid in the environment might be one of the most important factors controlling *C. albicans* infection.

Non-*Candida* fungal–bacterial interactions

Malassezia species are dimorphic yeast-like fungi that reside primarily on mammalian skin. These species require exogenous lipids for growth and are not often cultured from clinical samples because most diagnostic growth media lacks the appropriate supplements. Curvale-Fauchet *et al.* [27] examined the colonization of intravascular catheters by *Malassezia* species using lipid-containing media and found a 0.7% rate of infection. Four of the seven *Malassezia*-positive cultures also yielded bacteria, including coagulase-negative *Staphylococcus* and other uncharacterized Gram-negative bacteria. These results suggest that fastidious fungi might be present in other infection cases and that they could be part of a mixed bacterial–fungal biofilm. The role of these fungi in the formation of mixed biofilms or in the colonization of indwelling medical devices has not yet been examined and warrants further investigation. Large-scale profiling of fungal species in host-associated environments will provide important information about the diversity and distribution of fungi in both healthy humans and in other patient populations.

Cryptococcus neoformans is a common environmental fungus that is an opportunistic pathogen of immunocompromised patients. The ability to produce melanin pigments appears to provide protection against some environmental stresses and might play a role in *C. neoformans* virulence [28]. Frases *et al.* [29•] found that *Klebsiella aerogenes* is able to provide *C. neoformans* with the precursors that it requires for melanin synthesis. These precursors appear to be somewhat specific as *Escherichia coli*, *Serratia marcescens* and two *Enterobacter* species were unable to induce *C. neoformans* melanization. This provides evidence for a direct link between members of the microflora and the production of factors important for virulence by the fungus. A survey of other bacteria from the host could give us more information as to the pervasiveness of this particular type of interaction.

Recent studies have examined the association between *Aspergillus* and other infectious agents in the context of respiratory infections [30–32]; however, none of these studies carefully examines whether *Aspergillus* generally predisposes patients to bacterial infections, or if colonization by certain bacteria is specifically enhanced by co-infection with the fungus. Further examination of these interactions should give us an understanding of the specificity and clinical relevance of these findings.

Fungal–bacterial interactions also occur in skin and nail infections. Foster *et al.* [33] noticed that both dermatophyte and non-dermatophyte fungi grew poorly in the presence of *P. aeruginosa*, and showed that large *P. aeruginosa* populations in infected nails resulted in a lower fungal population. Interestingly, it appears as if the growth of P. aeruginosa is initially promoted by the

presence of the fungal community and, in this way, for the fungal community sets the stage for their own demise as the *P. aeruginosa* population increases in size. A model of the dermatophyte–*Pseudomonas* interaction might be of value for both basic research questions and to test clinical hypotheses.

Many of the above interactions suggest that some bacteria can have common interactions with a wide range of fungi. For example, the opportunistic pathogen *P. aeruginosa* appears to inhibit the growth of both *C. albicans* and dermatophyte fungi. Such interactions could have evolved through competition with fungi in the soils, in association with plants, or in the context of host-associated infections. For those bacteria that have common interactions with diverse fungi, investigation of fungal–bacterial association in non-clinical systems could provide important insights into these interactions.

Bacterial–fungal interactions in non-medical systems

There are many *in vitro* models examining fungal–bacterial interactions that focus on food microbiology, soil ecology, bacterial biocontrol of fungal pathogens, and bacterial–fungal interactions during mycorrhiza formation. We highlight some recent studies from these non-clinical fields that both capture the range of interactions and suggest avenues that need to be investigated using clinical fungal–bacterial models.

Ström *et al.* [34•] used a simplified system, comprised of the fungus *Aspergillus nidulans* and the Gram-positive bacteria *Lactobacillus plantarum* to investigate the effects of the bacteria on the fungus. The presence of *L. plantarum* alters the morphology of *A. nidulans* and leads to a decrease in growth rate. In response to *L. plantarum*, or to specific combinations of low-molecular weight products that it produces which are known to affect fungal growth, *A. nidulans* protein profiles on 2D-PAGE show the alteration in quantity and/or migration of two proteins. One is an unknown protein (named LbuA) and the other has 64% homology with an NADH-ubiquinone oxidoreductase (LbsA). This system seems ripe for microarray analysis in order to further understand the fungal response to this bacteria and its products. These studies might also provide additional insights into the ways that *Lactobacillus* species might inhibit *C. albicans* proliferation in the gut.

Listeria monocytogenes is a common contaminant of many types of food, especially dairy. To find yeasts that are effective for the inhibition of *L. monocytogenes*, Goerges *et al.* [35] screened 404 yeast strains, mostly isolated from smear-ripened cheeses, for anti-listerial activity. Three *Candida intermedia* strains and one *Kluyveromyces marxianus* strain were able to inhibit *L. monocytogenes* growth. The, as yet, unidentified molecule(s) should provide information about the maturation of mixed microbial communities in dairy products, and could have important implications for understanding the effects of fungi on bacteria within microbial communities.

The interaction between *Saccharomyces cerevisiae* and *Pseudomonas putida* was analyzed by Romano and Kolter [36]. It was found that *S. cerevisiae* could promote *P. putida* survival in high-glucose environments by quickly metabolizing glucose, leading to a lower availability of glucose for the bacteria. *P. putida* appears unable to control the activity of its periplasmic glucose dehydrogenase resulting in over-production of gluconate, which acidifies the medium when cells are grown in high-glucose concentrations. The low pH inhibits *P. putida* growth as well as exopolysaccharide production. Such simple physiological enablement, resulting in the modification of the nutrient environment, could form the foundation for a number of fungi–bacteria interactions and permit higher levels of microbial diversity in certain niches. Fusaric acid produced by the plant-pathogenic fungus *Fusarium oxysporum* is capable of directly regulating transcription of a number of genes involved in the *Pseudomonas chlororaphis* pyocyanin pathway [37]. Both of these studies, along with the previously described studies on butyrate [25•] and other LAB products [34•], suggest that many bacterial interactions with fungi might be mediated by what appear to be simple metabolic byproducts.

The study of mycorrhizal interactions has provided much of the driving force behind the bulk of the fungi–bacteria–host interaction literature although, in these cases, the hosts are plants. Mycorrhizas are symbiotic associations between plants and filamentous fungi that aid the plant in acquisition of nutrients and possibly provide protection from pathogens. Bacteria participate in this system either directly within the mycorrhizas or on the surface of the fungal filament. There appears to be communication between all of the members of these communities. The ability to isolate individual members and grow them axenically, before then mixing them allows a reconstitution of an association network that is functionally complete, but greatly simplified compared to the original soil community. Much work has been focused on the role of bacteria in helping or hindering establishment of these mycorrhizal interactions. In one specific example, bacterial-induced (*Streptomyces* AcH505) changes in mycorrhiza fungal (*Amanita muscaria*) gene expression were examined [38]. They noted alteration in a number of genes including those related to metabolism, signal transduction, and the transport of small molecules. Induction of PKA (protein kinase A) pathway genes in response to the presence of the bacteria might be suggestive of a change not only in metabolism but also in the cell cycle and/or cell morphology. The cAMP-PKA system is a central regulatory pathway that is well conserved among fungi. Although the mechanism by which this pathway is affected in *Amanita* species has not been

examined, it would be interesting to determine if the cAMP-PKA pathway is similarly affected in other fungi during interactions with bacteria.

Conclusions and future directions

Initial steps have been made in the analysis of fungal–bacterial interactions and their role in infection, but there remains a myriad of unanswered questions that will require the collaboration of mycologists, microbiologists, cell biologists and clinicians to answer in full. There are numerous reports that describe data on both fungal and bacterial infections around the world; however, most of these studies do not specifically analyze co-infection data. This clinical knowledge would not only inform us of the basic biology of mixed infections, but would also provide a useful knowledgebase for the clinician. If certain species combinations are never detected, which perhaps suggests an antagonistic relationship between organisms, researchers could be guided towards novel control mechanisms that could be exploited to treat infections. The interactions between fungi and bacteria in natural settings are complicated by a number of factors including host response, environmental parameters, and species composition of the community. Therefore, *in vitro* systems are necessary for a thorough understanding of fungal–bacterial interactions.

The animal body is not the only environment in which fungi and bacteria interact to help or harm their hosts. The studies of plant fungal pathogens and mycorrhizal interactions and the role of bacteria in these systems provide a theoretical framework for analysis of mammalian systems. The mechanisms used by fungi and bacteria in their association with the plant might not be very different from those used on and within the mammalian host.

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