MINIREVIEW

Cross-kingdom interactions: *Candida albicans* and bacteria

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Abstract

Bacteria and fungi are found together in a myriad of environments and particularly in a biofilm, where adherent species interact through diverse signaling mechanisms. Yet, despite billions of years of coexistence, the area of research exploring fungal–bacterial interactions, particularly within the context of polymicrobial infections, is still in its infancy. However, reports describing a multitude of wide-ranging interactions between the fungal pathogen *Candida albicans* and various bacterial pathogens are on the rise. An example of a mutually beneficial interaction is coaggregation, a phenomenon that takes place in oral biofilms where the adhesion of *C. albicans* to oral bacteria is considered crucial for its colonization of the oral cavity. In contrast, the interaction between *C. albicans* and *Pseudomonas aeruginosa* is described as being competitive and antagonistic in nature. Another intriguing interaction is that occurring between *Staphylococcus aureus* and *C. albicans*, which although not yet fully characterized, appears to be initially synergistic. These complex interactions between such diverse and important pathogens would have significant clinical implications if they occurred in an immunocompromised host. Therefore, understanding the mechanisms of adhesion and signaling involved in fungal–bacterial interactions may lead to the development of novel therapeutic strategies for impeding microbial colonization and development of polymicrobial disease.

Introduction

Candida albicans, a commensal fungal species commonly colonizing human mucosal surfaces, has long been adapted to the human host and has evolved because of the specific demands of the human host environment (Calderone, 2002). Distinctively, under conditions of immune dysfunction, colonizing *C. albicans* strains can become opportunistic pathogens causing recurrent mucosal and life-threatening disseminated infections with high mortality rates (Perlroth *et al.*, 2007). The increasing emergence of strains of *C. albicans* resistant to the commonly used antifungal agents has made clinical management of candidiasis increasingly difficult and the need for improved drug therapies crucial (Perlroth *et al.*, 2007).

Adherence to tissue is a prerequisite for colonization and infection and *C. albicans* cells interact with a wide variety of host extracellular matrix molecules that promote adhesion to host surfaces (O'Sullivan *et al.*, 2000; Cannon & Chaffin, 2001; Jenkinson & Douglas, 2002). The ability of *C. albicans* to switch its morphology between yeast and hyphal form is crucial to its ability to adhere to surfaces and colonize tissue (Calderone, 2002; Saville *et al.*, 2003).

In most natural environments, microorganisms exist predominantly as biofilms rather than as planktonic or free-floating cells (Douglas, 2003; El-Azizi *et al.*, 2004). Microbial biofilms are defined as structured microbial communities that are attached to natural or abiotic surfaces encased in a matrix of exopolymeric material consisting of a single microbial species or a mixture of bacterial or fungal species (Lewis, 2001; Douglas, 2003; Costerton *et al.*, 2005; Wargo & Hogan, 2006; Lynch & Robertson, 2008). This mode of life carries important clinical repercussions as it is now estimated that a significant proportion of all human microbial infections involve biofilm formation, particularly those formed on indwelling medical devices such as catheters and prostheses (Douglas, 2003; Ramage *et al.*, 2004).

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Crucially, biofilm-embedded organisms tend to exhibit increased resistance to antimicrobial therapy and to withstand host immune defenses (Costerton *et al.*, 1999; Lewis, 2001).

The biofilm of *C. albicans* sometimes exists in a heterogeneous mixture where it is intimately involved with other microbial species in this environment. In their attachment, cell aggregation and competitive inhibition for attachment sites take place in these mixed biofilms (Wargo & Hogan, 2006; Lynch & Robertson, 2008). Alternatively, the complex structure of the biofilm allows some degree of interspecies cooperation to develop between the populations and a range of metabolic interactions have been observed among microorganisms in biofilms, including mutualistic and commensal relationships (Romano & Kolter, 2005; Seneviratne *et al.*, 2008). An example of such a beneficial interaction was demonstrated by Romano & Kolter (2005) where a favorable effect on bacterial physiology and survival was mediated by the ability of the fungus to metabolize the available glucose, with consequent effects on the medium's pH.

Previous studies of biofilm development and species interaction have focused largely on bacterial species and despite billions of years of coexistence, far less is known about bacterial–fungal interactions within the biofilm communities. However, there is mounting interest in the study of *Candida*–bacteria interactions, which may range from simple antagonism and parasitism, to more intimate associations of pathogenesis and endosymbiosis (Hogan & Kolter, 2002; Jenkinson & Douglas, 2002; Hogan *et al.*, 2004; Costerton *et al.*, 2005). In fact, in the host environment, *C. albicans* is often found with bacterial species in polymicrobial biofilms where extensive interspecies interactions are likely to take place that may impact the *C. albicans* transition between virulent and nonvirulent states (Douglas, 2002). More importantly, drug susceptibility studies further indicated that fungal cells may modulate the action of antibiotics and that, conversely, bacteria can affect antifungal activity (Jenkinson & Douglas, 2002).

Although *in vivo* studies of polymicrobial infections have been lacking, preliminary *in vitro* work has demonstrated extensive interspecies interactions in these adherent populations. Klotz *et al.* (2007) studied the interactions of *C. albicans* with bacteria that form mixed microbial aggregates. The findings from the study demonstrated that mixed microbial aggregates form rapidly incorporating bacterial cells (Klotz *et al.*, 2007). *Candida albicans* agglutinin-like sequences (Als), cell-surface glycoproteins implicated in the process of adhesion to host surfaces, were identified to be important for the coadhesion of mixed microbial communities in biofilms and on mucus surfaces (Klotz *et al.*, 2007). Similarly, using a tube model to study the interactions between *Candida* and several bacterial species in biofilms, a study by El-Azizi *et al.* (2004) demonstrated a reduction in *C. albicans* adherence when bacteria and *C. albicans* are added simultaneously, indicating that adherent isolates compete for available sites.

In a biofilm environment, microbial species are highly interactive and use a range of cell-to-cell communication or 'quorum-sensing' (QS) systems. This phenomenon for promoting collective behavior within a population enhances access to nutrients and niches, as well as providing them with a collective defense against other competitor organisms (Hogan, 2006; Nikolaev & Plankunov, 2007; Williams, 2007). Therefore, they are capable of complex patterns of cooperative behavior that result from the coordination of the activities of individual cells (Nikolaev & Plankunov, 2007; Williams, 2007).

Although QS has primarily been studied in the context of single species, the expression of QS systems may be manipulated by the activities of other microorganisms within complex microbial consortia, which use different QS signals. Bacteria and fungi are found together in a myriad of environments, and although eukaryotes and prokaryotes have evolved diverse signaling mechanisms to respond to each other, the process of QS has only recently been shown to cross the prokaryote–eukaryote boundary (Hogan & Kolter, 2002; Joint *et al.*, 2002; Hogan, 2006; Williams, 2007). The area of research exploring this interkingdom interface is still in its infancy, yet studies describing the occurrence of both synergistic and antagonistic interactions between diverse microbial species are on the rise.

More importantly, evidence indicates that bacteria may play an important role in the pathogenesis of *C. albicans* infections. For example, prior urinary tract infection with *Escherichia coli* that agglutinates *C. albicans in vitro* was found to enhance adhesion of *C. albicans* to bladder mucosa and increase the likelihood of ascending infection by *C. albicans* (Levison & Pitsakis, 1987). In contrast, indigenous intestinal microbial communities reduced the mucosal adhesion of *C. albicans* to the gastrointestinal tract of hamsters by forming a dense layer of bacteria in the mucus gel, outcompeting yeast cells for adhesion sites and producing substances inhibitory to the adhesion of *C. albicans* (Kennedy & Volz, 1985). Therefore, alterations in the normal bacterial flora such as the result of treatment with broad-spectrum antibiotics, allow *C. albicans* to proliferate and invade tissues, greatly affecting the pathogenicity of *C. albicans* (Kennedy & Volz, 1985).

In addition, fungal–bacterial interaction has been shown to occur in patients in several other clinical conditions. A study by Pate *et al.* (2006) was aimed at estimating the propensity of keratomycosis (fungal eye infection) for parallel or secondary bacterial infection and at exploring affinities between fungal and bacterial coisolates. Results from that study demonstrated that 20% of keratomycoses cases studied consisted of polymicrobial infections,

indicating a high risk of bacterial coinfection with yeast keratitis, often complicating candidal keratitis (Pate *et al.*, 2006). Therefore, the significance of the clinical implications of the interactions between *C. albicans* and bacteria underlines the importance of studying these interactions to fully understand the microbial contribution to disease in polymicrobial infections.

Synergistic vs. antagonistic interactions

A good example of mutually beneficial interaction is coaggregation, a phenomenon that takes place in oral biofilms (Jenkinson & Douglas, 2002; Rickard *et al.*, 2003; El-Azizi *et al.*, 2004). The oral cavity comprises diverse microenvironments containing a range of surfaces to which microbial cells can adhere and accumulate on surfaces, including dental and mucosal tissues or prostheses such as dentures (Cannon & Chaffin, 2001; Jenkinson & Douglas, 2002; Ramage *et al.*, 2004). The survival of *C. albicans* in the host requires that a niche be established within these mixed-species communities of bacteria, and, therefore, intermicrobial binding (coaggregation or coadhesion) between *C. albicans* and oral bacteria is crucial for *C. albicans* colonization and persistence within complex microbial biofilms (Cannon & Chaffin, 2001; Jenkinson & Douglas, 2002).

Candida albicans adheres to a range of salivary pellicle components including proline-rich proteins and statherin, and the adhesion of *C. albicans* to saliva-coated surfaces is an important early step in its colonization of the oral cavity (Holmes *et al.*, 1995; O'Sullivan *et al.*, 2000; Cannon & Chaffin, 2002; Jenkinson & Douglas, 2002). However, because many species of oral bacteria bind similar components, they may compete with *C. albicans* for primary adhesion receptor sites (Holmes *et al.*, 1995, 2006; Basson, 2000; Jenkinson & Douglas, 2002). In addition to oral surfaces, *in vitro* and *in vivo* studies have demonstrated that *C. albicans* also adheres to the major microbial constituents of early dental plaque, such as streptococci and *Actinomyces naeslundii,* as well as to later colonizers such as *Fusobacterium nucleatum* (Bagg & Silverwood, 1986; Holmes *et al.*, 1996; Grimaudo & Nesbitt, 1997; Jabra-Rizk *et al.*, 1999). This ability of *C. albicans* to adhere to preattached organisms is an obvious advantage if it is not present in sufficiently high numbers, or lacks a sufficiently high affinity for adhesion sites to compete with the primary colonizers (Bagg & Silverwood., 1986; O'Sullivan *et al.*, 2000).

The interactions between yeast and streptococci appear to be essentially synergistic, where, in addition to providing adhesion sites, the streptococci excrete lactate that can act as a carbon source for yeast growth (Jenkinson *et al.*, 1990; Holmes *et al.*, 2006). *Candida albicans*, on the other hand, in addition to reducing the oxygen tension to levels preferred by streptococci, may provide growth stimulatory factors for the bacteria as a result of nutrient metabolism (O'Sullivan *et al.*, 2000; Jenkinson & Douglas, 2002). Although streptococcal species, namely *Streptococcus gordonii*, *Streptococcus oralis* and *Streptococcus sanguinis*, exhibit the highest affinities for *C. albicans*; *C. albicans* as well as *Candida dubliniensis* have been shown to coaggregate with *Fusobacterium* species in suspension (Grimaudo *et al.*, 1996; Grimaudo & Nesbitt, 1997). These latter interactions were inhibited by mannose, and therefore were thought to involve a protein component on *Fusobacterium* binding to a carbohydrate (mannan) receptor on the *Candida* cell surface (Jabra-Rizk *et al.*, 1999). In contrast, a study demonstrating the ability of *Actinomyces* to coaggregate with *C. albicans in vitro*, identified the receptors to be a protein moiety on the *Candida* surface, interacting with a carbohydrate-containing molecule on the surface of the *Actinomyces* (Grimaudo *et al.*, 1996).

In addition to these bacterial species, *C. albicans* is also frequently isolated with *Peptostreptococcus micros* in mixed infections from root canal samples in patients with persistent endodontic infections, suggesting that *Candida* may play a role in therapy-resistant apical periodontitis and root canal infections with pulp necrosis (Jabra-Rizk *et al.*, 2001; Lana *et al.*, 2001). Furthermore, the ability of *C. albicans* to cocolonize with streptococci and, to grow and survive at low pH (< 4.5) suggests that active carious lesions may harbor *C. albicans* (Jenkinson & Douglas, 2002). In fact, evidence shows that there is a higher incidence of *Candida* in groups with higher susceptibility to caries (Jenkinson & Douglas, 2002).

The range of intergeneric coaggregations occurring between *C. albicans* and oral species possibly play an important factor in *C. albicans* colonization in the oral cavity (Jenkinson & Douglas, 2002). More importantly, the most serious ramifications of these fungal–bacterial interactions with clinical implications comes from the findings demonstrating that the physical interactions between *C. albicans* yeasts and hyphae with oral streptococci, increased tolerance of the polymicrobial biofilm to antimicrobial agents and enhanced resilience to physical disruption (Jenkinson & Douglas, 2002). Therefore, understanding the complex mechanisms by which *Candida* and oral bacteria cocolonize, will assist in the development of new protocols to block adhesive reactions and eliminate *Candida* from biofilm-related oral infections. Furthermore, understanding the molecular basis of the decreased drug sensitivity of *C. albicans*, the result of its interaction with oral bacteria, will aid in the future development of more powerful ways to combat the rise in antifungal resistance.

Perhaps the best characterized example of an antagonistic fungal–bacterial interaction is the one described between *C. albicans* and the opportunistic bacterial pathogen *Pseudomonas aeruginosa* (Hogan & Kolter, 2002; Cugini *et al.*,

2007; McAlester *et al.*, 2008; Williams & Cámara, 2009). Recently, a set of studies on the interactions between these two species revealed that *P. aeruginosa* forms a dense biofilm on *C. albicans* hyphae and kills the fungus (Hogan & Kolter, 2002) (Fig. 1). By contrast, the bacteria were unable to bind to or kill the yeast form of *C. albicans*, and hyphal death occurred only after the onset of biofilm formation (Hogan & Kolter, 2002). Using a set of *P. aeruginosa* mutants, Hogan & Kolter (2002) demonstrated that several *P. aeruginosa* virulence factors, including pili and secreted molecules, were acting in concert to kill *Candida* hyphae These findings suggest that microbial virulence factors might also be involved in bacterial–fungal interactions and that antagonism between bacteria and fungi may contribute to the evolution and maintenance of many pathogenesis-related genes. Furthermore, in similar studies, *C. albicans* morphology was reported to be significantly affected by the presence of *P. aeruginosa*; *C. albicans* yeast cells were capable of suppressing filamentation upon exposure to a *P. aeruginosa* QS molecule (3-oxo-C12 homoserine lactone) (Hogan *et al.*, 2004; Williams & Cámara., 2009). Similar to *P. aeruginosa*, *C. albicans* uses secreted signals to regulate gene expression and virulence. Most notably, *C. albicans* yeast cells were recently shown to secrete farnesol, a 12-carbon sesquiterpene, which acts as a virulence factor and a repressor of the switch from yeast to hyphal growth (Hornby *et al.*, 2001; Ramage *et al.*, 2002).

Interestingly, the activity of farnesol is compared with that of the *P. aeruginosa* 3-oxo-C12 homoserine lactone molecule, also a molecule with a 12-carbon backbone (Hogan *et al.*, 2004; Williams & Cámara., 2009). Therefore, the response of *C. albicans* induced by farnesol may represent a fungal strategy for survival in the presence of antagonistic microorganisms such as *P. aeruginosa*, particularly within the context of biofilm. Furthermore, it was established that signaling is bidirectional and that the *C. albicans* molecule farnesol not only inhibits *P. aeruginosa* pyocyanin production, which is toxic to *C. albicans*, but also inhibits swarming motility in *P. aeruginosa* (Cugini *et al.*, 2007; McAlester & Cámara., 2008; Williams *et al.*, 2009). Combined, these findings support the notion that eukaryotes and prokaryotes possess diverse signaling mechanisms to detect and respond to each other through QS signal molecules (Joint *et al.*, 2002; Dudler & Eberl, 2006; Williams 2007; Kobayashi, 2009). These interactions between *P. aeruginosa* and *C. albicans* may reflect the relationships of bacterial and fungal species that coexist in other environments.

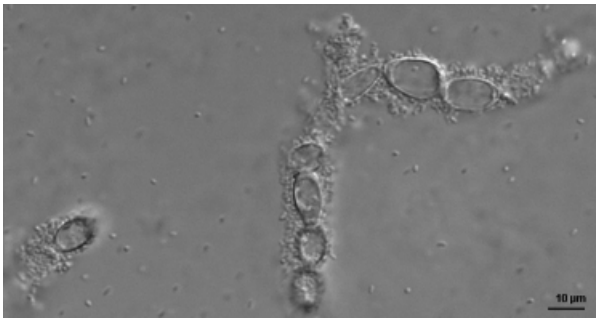

Fig. 1. Differential interference contrast microscopic image of a mixed-species biofilm demonstrating extensive adherence of *Pseudomonas aeruginosa* to *Candida albicans*.

More importantly, several studies suggest that *P. aeruginosa* and *C. albicans* interact with each other in the human body, as they are commonly found in mixed infections (Williams & Cámara., 2009). Gupta *et al.* (2005) studied the effect of various bacterial species collected from burn wounds on the growth of *Candida* sp. to determine whether the presence of bacteria affects the growth of *Candida* sp. in patients. Confirming the *in vitro* observations, results of the analysis revealed that the presence of *Pseudomonas* sp. invariably inhibited *Candida* sp. growth. Thus, the authors concluded that the absence of *Candida* sp. in burn wounds, where *Pseudomonas* sp. is present, may be due to the inhibition of *Candida* growth by *Pseudomonas* sp. The establishment of an interaction between *C. albicans* and *P. aeruginosa in vivo* holds significant clinical implications, as these two species are frequently coisolated from cystic fibrosis patients, a critically ill patient population that often succumbs to opportunistic infections (Kerr, 1994).

A seemingly similar antagonistic interaction between *C. albicans* and the bacterial pathogen *Acinetobacter baumannii* was recently reported. Using the nematode *Caenorhabditis elegans* as a coinfection host, Peleg *et al.* (2008) demonstrated that, similar to *P. aeruginosa*, *A. baumannii* exhibited a predilection for *C. albicans* filaments and inhibited *C. albicans* filamentation, resulting in attenuated virulence of *C. albicans* in the nematode. More interestingly, *C. albicans* was able to inhibit *A. baumannii* growth via farnesol production (Peleg *et al.*, 2008).

A more clinically significant yet not fully elucidated fungal–bacterial interaction is that occurring between *C. albicans* and staphylococci (Tawara *et al.*, 1996; Ishihara *et al.*, 2000; Adam *et al.*, 2002; Baena-Monroy *et al.*, 2005). staphylococci and *Candida* species are receiving renewed attention because of the escalating development of antimicrobial resistance and the increasing involvement of biofilms in chronic and systemic infections (Perlroth *et al.*, 2007). In fact, these species are currently the leading pathogens in bloodstream and systemic infections and a major cause of morbidity and mortality in hospitalized patients (Perlroth *et al.*, 2007). An indication of the existence of a unique and intricate relationship between *C. albicans* and *Staphylococcus aureus* was recently demonstrated *in vitro* in our laboratories (M.A. Jabra-Rizk & M.E. Shirtliff, unpublished data), where FISH studies revealed extensive physical interactions

between the staphylococci and both yeasts and hyphae in the mixed species biofilms (Fig. 2), similar to what was previously shown with scanning electron microscopy (Costerton *et al.*, 1999; Adam *et al.*, 2002) (Fig. 3). In addition, global gene and protein expression studies demonstrated differential expression by each species when grown in mixed biofilms, establishing the occurrence of a dynamic and interactive process between these two pathogens as they coexist (unpublished data). More importantly and similar to the observations made with *C. albicans* and oral streptococci biofilms on denture acrylic, drug susceptibility studies suggested that fungal cells can modulate the action of antibacterial agents and staphylococci can affect the activity of antifungal agents in these biofilms (Adam *et al.*, 2002; Jenkinson & Douglas, 2002). Furthermore, El-Azizi *et al.* (2004) reported that staphylococcal proteinase enhanced adhesion of *C. albicans* to buccal mucosa.

Several other studies investigated the cocolonization or coinfection of these two species in a clinical setting. A recent study by Baena-Monroy *et al.* (2005) investigating oral colonization and denture stomatitis caused by *Candida* and staphylococci in denture wearers, demonstrated a high incidence of mixed colonization by both species; *C. albicans* was isolated from 66.7% of the subjects and *S. aureus* from 49.5% of the same prostheses. In a similar study by Tawara *et al.* (1996), all saliva samples from 29 patients whose dentures carried *Staphylococcus* species and *C. albicans* were also found to contain both microorganisms.

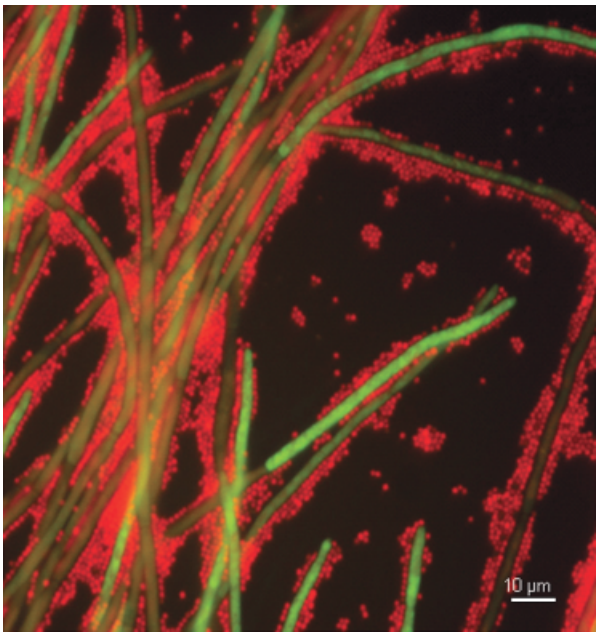

Fig. 2. FISH image of *Candida albicans* and *Staphylococcus aureus* mixed-species biofilm using fluorescein and Tamra-labeled species-specific peptide nucleic acid probes demonstrating extensive adherence of the bacteria to *C. albicans* hyphae.

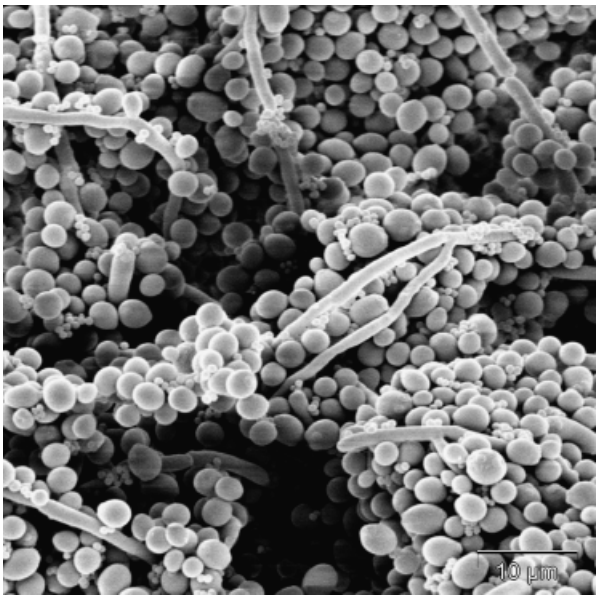

Fig. 3. Scanning electron micrograph of a mixed-species biofilm of *Candida albicans* and *Staphylococcus epidermidis*. Smaller bacterial cells can be seen adherent to both yeasts and hyphae.

The significance of the implications of this interaction between these species in a more vital clinical setting was perhaps established by a study performed by Costerton *et al.* (1985). Scanning electron micrographs from that study revealed a mixed biofilm of both species that had formed on the plastic surface of an intracardial Hickman catheter removed from a patient. The same organisms were isolated from blood cultures when the patient developed septicemia (Costerton *et al.*, 1985).

In cases of ventilator-associated pneumonia, the early onset phase was shown to be associated with *S. aureus* and other bacteria, whereas late onset of disease, in addition to bacteria, is also associated with *Candida* sp. (Timsit *et al.*, 2001). Furthermore, mixed bacterial–fungal biofilms have been shown to be associated with a multitude of other conditions including infections of endotracheal tubes, biliary stents, silicone voice and orthopedic prostheses and acrylic dentures (Costerton *et al.*, 1999; Ramage *et al.*, 2004).

Candida albicans has been shown to stimulate infection in mice by a number of bacteria. Carlson (1983a, b) described a synergistic effect between *C. albicans* and *S. aureus* on mortality of mice when dually infected. In these studies, mice inoculated intraperitoneally with sublethal combinations of *C. albicans* and *S. aureus* at doses that separately caused no animal deaths, resulted in 100% mortality. The reasons behind the strong amplifying effect of *C. albicans* on the virulence of *S. aureus* are not clear. It is conceivable, however, that the candidal infection process causes physical damage to organ walls, allowing other microorganisms to

penetrate more easily. In fact, studies have shown that bacteria penetrate organs more easily in the presence of *C. albicans*. On the other hand, it is also possible that *C. albicans* directly stimulates the growth of *S. aureus*, as was shown *in vitro* (Carlson, 1983a, b). This collective ability to damage tissue would explicate the severity and rapid progression of their coinfection. Were this extensive affinity between *S. aureus* and *C. albicans*, and the amplification of the virulence of *S. aureus* (the result of its coexistence with *C. albicans*), also to take place in humans who harbor candidal infections, the medical implications would be great.

Alternatively, although the initial observed interaction between *C. albicans* and *S. aureus* seem to be synergistic, it is possible that at some point during the development of the biofilm, the relationship becomes competitive or antagonistic. Investigations in our laboratories have demonstrated that the candidal QS molecule farnesol affects biofilm formation by *S. aureus*, as well as compromises cell membrane integrity, viability and susceptibility to a variety of clinically important antibiotics (Jabra-Rizk *et al.*, 2006). These findings suggest a possible role for farnesol in orchestrating the interaction between *C. albicans* and *S. aureus* within a mixed biofilm.

The coinfection of *C. albicans* and *S. aureus* represents a significant therapeutic challenge and their coisolation from blood is an indication of dire prognosis, especially within the context of an underlying immunocompromising condition (Pittet *et al.*, 1993; Adam *et al.*, 2002; Wisplighoff *et al.*, 2004). Therefore, characterizing the nature of the complex interaction between these two microbial species is the first step in understanding the nature of their coexistence in the host.

Conclusion and future perspectives

Bacteria are often found with *Candida* species in polymicrobial biofilms *in vivo*. Polymicrobial diseases represent the clinical and pathological manifestations induced by the presence of multiple infectious agents and are referred to as complex, complicated, mixed, dual, synergistic or concurrent (Pittet *et al.*, 1993; Tuft, 2006). The presence of a polymicrobial infection has important implications for management because it will modify the clinical course of the disease, impacting the selection of antimicrobial therapy and the anticipated response to treatment, especially when it involves pathogens commonly exhibiting antimicrobial resistance (Pittet *et al.*, 1993; Jenkinson & Douglas, 2002). Yet, despite the gravity of such infections, areas of study in polymicrobial diseases are in their infancy.

The biological relevance of interdomain microbial interactions remains largely unknown. A deeper understanding of the mechanisms of adhesion and signaling involved in bacterial–fungal interactions will provide a new perspective on the role of known virulence determinants and the factors relevant to polymicrobial disease. It may be possible by manipulation of adhesion interactions to modify colonization by *C. albicans* and thus impede the development of disease. To that end, future studies should focus on designing animal model systems to study *in vivo*-grown mixed bacterial–fungal biofilms to investigate the complex dynamics of polymicrobial infections.

The key challenges now are to determine mechanistically precise details of the unique biology of *C. albicans* and bacteria interaction under conditions of coexistence. With the application of powerful DNA microarray and proteomic technologies, the tools are now available to undertake such efforts. The ultimate aim will be to use the knowledge of these processes to develop novel therapeutics and other potential applications in biotechnology. Identification of potential targets for inhibition of coadhesion and biofilm development may ultimately provide means to modify microbial colonization and thus impede the development of polymicrobial disease.

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