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Candida albicans and *Enterococcus faecalis* in the gut Synergy in commensalism?

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The fungus *Candida albicans* and the gram-positive bacterium *Enterococcus faecalis* are both normal residents of the human gut microbiome and cause opportunistic disseminated infections in immunocompromised individuals. Using a nematode infection model, we recently showed that co-infection resulted in less pathology and less mortality than infection with either species alone and this was partly explained by an interkingdom signaling event in which a bacterial-derived product inhibits hyphal morphogenesis of *C. albicans*. In this addendum we discuss these findings in the context of other described bacterial-fungal interactions and recent data suggesting a potentially synergistic relationship between these two species in the mouse gut as well. We suggest that *E. faecalis* and *C. albicans* promote a mutually beneficial association with the host, in effect choosing a commensal lifestyle over a pathogenic one.

Polymicrobial Infections: An Understudied Clinical Problem

There has been a general awareness that polymicrobial infections—those in which more than one species are identified from clinical samples—are associated with worse clinical outcomes than monomicrobial infections for decades, though large-scale epidemiological studies are lacking.^{1–3} Our laboratories study two pathogens that are commonly found together in polymicrobial infections, the fungus *Candida albicans* and the gram-positive bacterium *Enterococcus faecalis*.

These two organisms trail only staphylococci in terms of prevalence in nosocomial sepsis and are frequently found together in clinical samples. While reports describing the co-isolation of these two species are common (see, for instance, refs. 4–6), one large-scale retrospective analysis of clinical samples illustrated the propensity of these species to be found together. Hermann, et al.⁷ separated 68,000 specimens from a two-year period at a large German teaching hospital into those with detectable *Candida* (~5,200) and those without, including samples from both sterile (blood, CSF) and non-sterile (feces, sputum, skin) sites. Overall, *E. faecalis* was twice as likely to be found in *Candida*-positive samples than *Candida* negative ones; enrichment of *E. faecalis* in the fungal samples was even more dramatic in blood samples and in patients in the ICU.⁷

The frequency with which the two species are cultured from the same samples may reflect their similar biology within the host, may be due to synergistic interactions, or some combination of the two. Both species commonly colonize the gastrointestinal and urogenital tracts of humans and are considered opportunistic pathogens, meaning that bloodstream infections are rare in the absence of an underlying immunological dysfunction. Whether they might specifically interact with each other to alter their commensal population size, propensity to disseminate, or inherent virulence properties had not been addressed, but were reasonable questions given the clinical significance of this specific polymicrobial infection.

Keywords: *Candida*, *Enterococcus*, *C. elegans*, microbiome, hyphal morphogenesis

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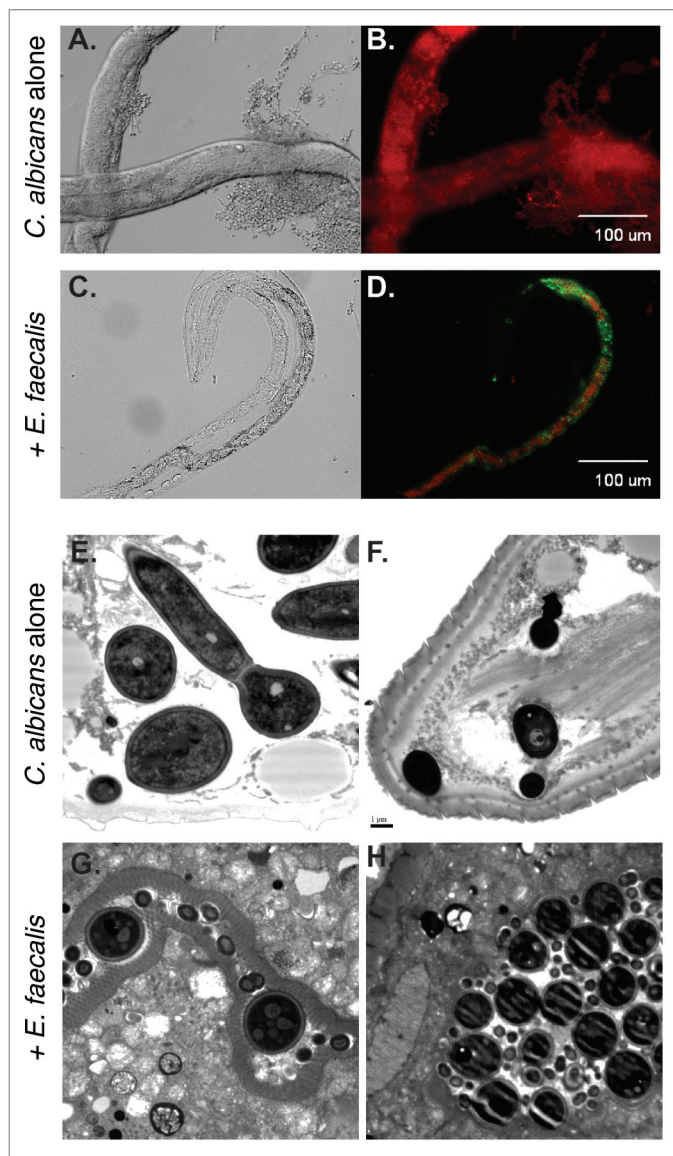


Figure 1. A *C. elegans* infection model reveals attenuation of virulence in *C. albicans*–*E. faecalis* coinfections. (A–D) Fluorescence imaging shows the two species mixing in the worm and the absence of hyphal growth in the coinfection. Worms were infected with yCherry labeled-*C. albicans* alone (A and B) or coinfecting with GFP-labeled *E. faecalis* (C and D) and imaged using DIC (A and C) or fluorescence (B and D). Panels (E–H) Ultrastructural analysis of nematode physiology. Worms were infected with *C. albicans* alone (E and F) or with both species (G and H) before processing for transmission electron microscopy. The disruption of the normal gut physiology in the *C. albicans*-infected worms relative to the coinfection is apparent. The scale bar in panel F is 1 μ m and applied to (E–H).

A Nematode Co-Infection Model Reveals Surprising Interactions

The model invertebrate *Caenorhabditis elegans* has been successfully employed as a system to study both bacterial and fungal pathogenesis,⁸ including for both *C. albicans* and *E. faecalis*.^{9,10} It offers numerous advantages in terms of ease of use, cost, ethical considerations and host genetics; most

importantly, it has identified factors known to be relevant to virulence in mammals including the FsrB quorum sensing system in *E. faecalis* and hyphal morphogenesis in *C. albicans*.^{9–11} This model has also been used to investigate polymicrobial infections between *C. albicans* and *Acinetobacter baumannii*.¹² These precedents encouraged us to examine the effects of co-infection by these two species in the worm model.¹³

In the laboratory, *C. elegans* are normally fed on a lawn of non-pathogenic *E. coli* grown on the surface of an agar medium. To prepare *C. elegans* for pathogen exposure, the worms are first allowed to develop on *E. coli* to the fourth larval stage (L4), which is the stage just before adulthood. Then the animals are transferred onto a lawn of pathogen. Survival is usually assayed over time on the solid medium.¹⁰ For infection with *C. albicans*, we followed a variation on this protocol, which involved moving the animals into liquid medium after a few hours of exposure to *C. albicans* on solid medium.^{12,13} For co-infection, we either exposed the animals to *E. faecalis* on solid medium before or after exposure to *C. albicans*.¹³ As expected, worms exposed to either species individually died far more quickly than those grown on the normal *E. coli* food source. This effect was particularly dramatic with *C. albicans*, where we observed florid hyphal growth that eventually penetrated the worm's cortex, as had been described.⁹ Next, we examined animals co-infected with both pathogens. Using fluorescently tagged cells, we showed that both species co-existed in the worm gut (Fig. 1). To our surprise, worms lived substantially longer when infected with both species relative to either one individually. The most dramatic effect was observed when the animals were first exposed to *E. faecalis* followed by *C. albicans*; worm survival was not statistically different from feeding on *E. coli*.¹³ The effect was not as dramatic when the order of exposure was reversed. Therefore it is possible that exposure to *E. faecalis* somehow primes the worm's innate immune system to better withstand a later exposure to *C. albicans*.

Another striking observation was that, no matter what the order of exposure, the presence of *E. faecalis* dramatically inhibited hyphal morphogenesis within the worm, reducing tissue damage. The intestinal pathologies seen with either pathogen alone were essentially absent in the co-infected animals (Fig. 1). Hyphal growth was also inhibited in mixed-species biofilms, but not in other strongly hyphal-inducing conditions in vitro, such as the presence of serum. The inhibition is mediated through a secreted compound

under the influence of the FsrB system, as sterilized supernatants from wild-type but not *fsrB*⁻ strains grown in media blocked morphogenesis and attenuated virulence of *C. albicans* in the worm model. Preliminary characterization indicated that the inhibitory compound is small and heat-stable. Its molecular identification is ongoing.¹³ Notably, other bacterial species also secrete compounds that affect *C. albicans* biology. Hyphal-inducing, hyphal-inhibiting and fungicidal activities have been observed, as will be summarized below.

However, this work leaves many questions beyond the nature of the inhibitory molecule. We cannot yet say how *C. albicans* attenuates *E. faecalis* killing in the worm or how the combination of the two species dramatically improves intestinal physiology. The applicability of these findings to virulence in a mammalian model has not been addressed either, though, as will be discussed below, there is some preliminary evidence in the literature of significant interactions between these two microbes in both a mouse infection model and a mouse commensal model.

Under the Influence: Secreted Bacterial Signals that Affect *C. albicans*

It has long been known that microbes secrete products that can kill one another, a byproduct of competition for resources in their ecological niches. We have harnessed the occurrence of these compounds to our advantage, and most of our antimicrobial medicines are derived from naturally occurring microbial products. But microbes also produce secreted signals with more subtle effects than growth inhibition or death. Because *C. albicans* lives in the mammalian host in environments rich with prokaryotes, it is not surprising that this fungus responds to signals secreted by bacteria. Most studies have focused on hyphal morphogenesis, an easily observable phenotype. The first bacterium discovered that affects *C. albicans* morphogenesis was *Pseudomonas aeruginosa*. The secreted signal was identified as 3-oxo-C₁₂ homoserine lactone (3C-HSL). HSLs are the primary molecules by which gram-negative species sense quorums, and

it was notable that *C. albicans* sensed and responded to this signal, as inter-kingdom signaling was not well appreciated at the time.¹⁴ The 3C-HSL resembles farnesol, a signaling molecule produced by *C. albicans* that inhibits hyphal formation through the Ras1-cAMP-Efg1 signaling pathway.^{15,16} Other gram-negatives such as *Burkholderia cenocepacia* and *Xanthomonas campestris* also inhibit *C. albicans* hyphal morphogenesis by producing decanoic acids that mimic the activity of farnesol.^{17,18} *P. aeruginosa* also releases toxic redox-active phenazines. At high concentrations, these compounds inhibit *C. albicans* growth, but recently, a new role has been discovered for phenazines at lower concentrations. They disfavor hyphal morphogenesis by inhibiting the respiratory chain; it is thought that the yeast form preferentially uses a fermentative mode of growth.¹⁹

P. aeruginosa, *A. baumannii* and *Salmonella typhimurium* can each inhibit the *Candida* hyphal morphogenesis that occurs in the *C. elegans* model. Depending on the organism, this activity is totally or partially dependent on a secreted substance. Surprisingly, the compound does not appear to be 3C-HSL, as addition of pure 3C-HSL did not inhibit filamentation in *C. albicans*-infected worms. Also, loss of the primary *A. baumannii* HSL synthase, encoded by *luxI*, had no effect on its ability to inhibit *Candida* filamentation.¹² The inhibition by *A. baumannii* appeared to be partly dependent on the bacterium preferably attaching to the hyphae, killing this morphotype.¹² *S. typhimurium* was also shown to inhibit hyphal morphogenesis in part by preferentially killing the hyphal form of *C. albicans*. In this case, the killing effect was not dependent on cell-to-cell contact and is due to an unidentified secreted substance found in stationary phase supernatants.²⁰

What about gram-positives other than *E. faecalis*? The staphylococci are not documented as affecting *C. albicans* hyphal morphogenesis, though there is evidence that they enhance biofilm formation when mixed with *C. albicans*.^{12,21} On the other hand, *Streptococcus mutans*, an oral microbe and the major etiological agent of cavities, was found to inhibit *C. albicans* hyphal morphogenesis in mixed species

biofilms²² and this effect is mediated via a secreted competence-stimulating peptide (CSP),²³ part of a family of small and often modified peptides commonly used for quorum sensing in gram-positive species. Not surprisingly, several other streptococcal species that generate this peptide were also able to inhibit *Candida* morphogenesis, including *S. gordonii*, *S. oralis*, *S. salivarius* and *S. sobrinus*. How this peptide exerts its effects on *Candida* remains mysterious.²³ Another report showed that a different *S. gordonii* strain actually enhanced *C. albicans* filamentation within biofilms in a mechanism somehow dependent on LuxS, which produces autoinducer-2.²⁴

In summary, secreted bacterial products from a variety of species can inhibit or promote *C. albicans* filamentation. In many cases, particularly with *Pseudomonas*, the evidence points to a direct antagonism between the species in vitro. Yet, in vivo, the picture appears more complex. *Pseudomonas* ventilator-associated pneumonia is both more likely and more severe if the patient is colonized by *Candida*.²⁵ The presence of *Pseudomonas* exacerbates tissue damage in a model of *Candida* infection of burn wounds.²⁶ Biofilms formed between *C. albicans* and either *S. aureus* or *S. gordonii* are larger and more drug resistant than their monomicrobial counterparts.^{24,27} Clearly there are context-dependent interactions that prevent simple conclusions about the in vivo effect of mixed infections. The nematode infection model is a step between in vitro assays and the more challenging mammalian models.

E. faecalis–*C. albicans* Interactions in the Mammalian Host

The data reported in Cruz, et al.,¹³ convincingly demonstrates that a co-infection of *C. albicans* with *E. faecalis* reduces tissue damage and extends lifespan of the worms relative to either monomicrobial infection. The presence of *E. faecalis* also dramatically lessens hyphal morphogenesis of *C. albicans*, a key virulence trait of this species.^{28,29} Moreover, this effect requires the *E. faecalis* Fsr two-component system, a central regulator of virulence in

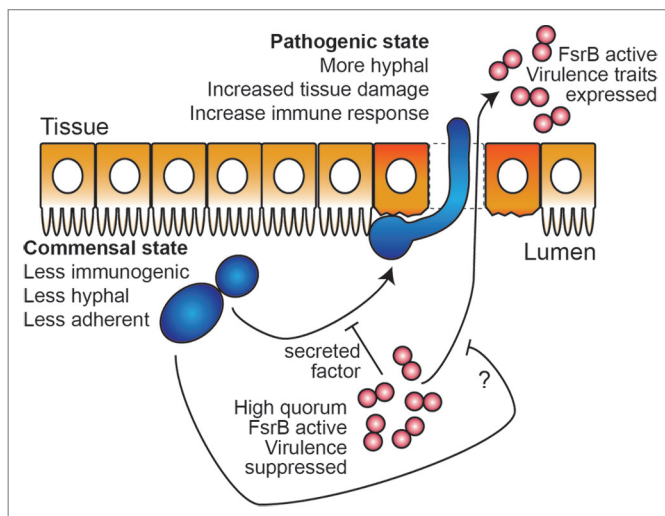


Figure 2. A speculative model for *Candida-Enterococcus* interactions in the gut. In the worm gut, *C. albicans* transitions from a commensal mode characterized by yeast-form growth to an invasive, hyphal and pathogenic state. This transition is inhibited by the presence of *E. faecalis* through molecule(s) secreted in an FsrB-dependent manner, thus maintaining the commensal association with the host. Likewise, mono-infection with *E. faecalis* imposes significant gut pathology, which is reduced in the presence of *C. albicans* through an unknown mechanism. In the mammalian gut, the work from Huffnagle and colleagues suggests that these two species also promote a commensal association with the host which we speculate can be disrupted by changes to microbe or host factors leading to infection. *C. albicans* cells are shown in blue, *E. faecalis* in red, and gut epithelial cells in orange.

mammalian models.³⁰⁻³² Thus, the phenomenon we have observed is closely associated with known virulence processes in both species.

Viewed through the traditional lens of microbial pathogenesis, our data showed a significant attenuation of virulence in the co-infection compared with the mono-infections. Yet, neither species tend to cause serious infections in healthy individuals, with the primary at-risk population being hospitalized and/or immunocompromised patients. Rather, in healthy people, both are primarily associated with the normal microbiota at multiple body sites, especially the gastrointestinal tract. So are the effects of this interkingdom co-infection really an attenuation of virulence? Perhaps *C. albicans* and *E. faecalis* have synergistic effects on colonization; that is, this interaction promotes a stable non-pathogenic association with the host.

Is there any evidence to support this idea? Yes, in fact, in striking work from Gary Huffnagle and colleagues at the University of Michigan, who have long been interested in the physiological effects of perturbing the gastrointestinal microbiota through the introduction of fungi.

The mouse is an ideal model for this work because common lab strains do not harbor *C. albicans* as a commensal (some other *Candida* species can occasionally be isolated), allowing investigators to experimentally manipulate the fungal component of the microbiota. Noverr and Huffnagle showed some years ago that the introduction of *C. albicans* to the gut of uncolonized mice had demonstrable effects on systemic immune responses.³³ Numerous studies have addressed the disruption of gut bacterial populations by antibiotic treatment and the subsequent recovery after cessation of the drug. These alterations are complex, dependent on the antibiotic and the individual, but the bacterial microbiota generally recovers with some loss of diversity (for a more detailed discussion, see ref. 34). Taking this one step further, Huffnagle asked whether the presence of *C. albicans* would alter the dynamics of bacterial recovery from antibiotic pressure.³⁵ Mice were given the broad-spectrum antibiotic cefoperazone for one week, at which point one group of animals were inoculated with *C. albicans* via intragastric gavage. The antibiotic was subsequently removed from both the

inoculated and control groups and bacterial colonization in the stomach was monitored seven and 21 d later. While there were substantial differences in the overall population structure in both antibiotic-treated groups relative to untreated controls, the real surprise came when they focused on the lactic acid bacteria. In the no-*Candida* group, *Enterococcus* species were the first to recover, but were replaced by lactobacilli within three weeks. In stark contrast, the *C. albicans*-treated animals remained dominated by *Enterococcus*, in particular by *E. faecalis*, the species that synergized with *C. albicans* in our studies in the worm gut.^{13,35} A subsequent study focused on the cecum showed very similar results.³⁶ Notably, *C. albicans*-induced gastritis was much worse in gnotobiotic mice than it was in antibiotic-treated normal mice, indicating that even an impaired bacterial microbiota can suppress *C. albicans*-associated pathology.³⁵

This work demonstrates that *C. albicans* promotes *E. faecalis* growth in the mammalian gastrointestinal tract, though it has not been determined whether this is through fungal antagonism of lactobacilli or synergism with enterococci. The latter would be consistent with our studies in *C. elegans*. Figure 2 presents a highly speculative model whereby interspecies interactions inhibit elaboration of virulence traits to promote a commensal interaction with the host. This working model serves as a basis for our future investigations and this model is complicated by the clinical picture, in which enterococci and *Candida* comprise polymicrobial infections associated with worse outcomes. Unfortunately, there is only one, decades-old, study in the literature that assesses the potential synergies between these two microbes in a mammalian infection model. Carlson infected mice by intraperitoneal injection with sub-lethal doses of *C. albicans* and *E. faecalis*.³⁷ Five days later, the animals were sacrificed and the blood, pancreas, kidney, spleen and peritoneum were assessed for CFUs of both *E. faecalis* and *C. albicans*. At doses of *E. faecalis* that do not normally cause detectable dissemination (10^7), the addition of *C. albicans* resulted in significant numbers of *E. faecalis* in all tissues tested. In fact, even with an inoculum as low as 10^3 , *E. faecalis* was

still detectable in some tissues. The synergism was not mutual; sublethal doses of the bacteria were not observed to stimulate *C. albicans* infectivity.³⁷ *C. albicans* enhancement of bacterial infection was not limited to *E. faecalis*, but also observed for *Staphylococcus aureus* and *Serratia marcescens*. A more recent study, examining the effects of *C. albicans* on *S. aureus* suggests that a heightened inflammatory response occurs when both microbes are injected together, which could account for the poorer outcome.³⁸

The Complete Microbiota

Interactions among and between microbial kingdoms certainly play key roles in the structure of the human microbiota and its influence on health. An emerging therapy for *Clostridium difficile* infections, which are particularly refractory to antibiotic therapy, is the reconstitution of the microbiota via fecal transplants from healthy donors (rev. in ref. 39). An alternative remedy for vaginal candidiasis is the topical application of yogurt with active lactobacilli (see ref. 40). A very recent study demonstrated a dramatic difference in the penile microbiome before and after circumcision that may underlie the different susceptibilities to HIV and other sexually transmitted diseases.⁴¹ There are and certainly will be additional examples of inter-microbial interactions that alter disease states or severity.

The move from culture-based to sequence-based determination of microbial populations has offered tremendous opportunities to understand the diversity, structure and dynamics of the microbiota. And, indeed, a vast array of literature has described the bacterial microbiome at various body sites, after specific iatrogenic interventions and during development. The questions being asked are so diverse that a recent paper compared the

microbiome of dog-owning families with their pets.⁴²

The specific and relevant interkingdom interactions we and others have identified between *C. albicans* and *E. faecalis*, *P. aeruginosa* and *S. aureus*, streptococci and others have come because *Candida* is a known component of the microbiota. Despite significant recent efforts to characterize the human-associated microbiome, our knowledge of the eukaryotic component remains rudimentary, because studies of the “complete” microbiome routinely focus on the bacterial-specific 16S rDNA, excluding eukaryotic microbes, both fungi and protozoans. This is fortunately changing thanks to the sequencing revolution: the landmark Human Microbiome Project, which characterized clinical specimens from 242 people, included some whole genome sequencing in which lower eukaryotes were identified, though most of the data were still based on 16S sequencing.^{43,44} A report describing the fungal microbiome of the skin appeared very recently, showing a community that differs both between individuals and between anatomical locations on the same person. Though dominated by species of the genus *Malassezia*, many fungal taxa were represented.⁴⁵ This is probably the most complete description of the fungal microbiome to date and hopefully these efforts will continue to increase our understanding of the diversity of the eukaryotic component.

What we do know of the eukaryotic microbiota hints at fascinating biology. *C. albicans* appears to have a molecular mechanism to suppress its own population size in the gut, for reasons unknown.⁴⁶ A limited study of the oral “mycobiome” from 20 individuals identified a total of 85 fungal genera, of which 15 were present in at least 20% of the subjects, with *Candida* as the most abundant.⁴⁷ Very

limited 18S sequencing in a handful of people has suggested that the most abundant eukaryote in the human gut is not *Candida*, but the protozoan *Blastocystis*, with *Galactomyces* as the predominant fungal species.⁴⁸ Neither species has been extensively studied. Patients with hepatitis B or with inflammatory bowel disease have a more diverse fungal community than healthy controls.^{49,50} Most recently, a polymorphism in Dectin-1, a β -glucan receptor critical for antifungal recognition, has been associated with severity of ulcerative colitis.⁵¹ How these organisms might affect the bacterial microbiome has simply not been addressed, but it is certainly reasonable to speculate that fungal burden and the composition of the microbiota contributes to the propensity to disseminate in at-risk patients.

In summary, our work has identified a specific interaction between *C. albicans* and *E. faecalis* that promotes the commensal form over the pathogenic, at least partly through suppression of fungal morphogenesis by a bacterially-derived molecule. This work is consistent with a potentially synergistic relationship between these two species uncovered by experimental manipulation of the murine gut^{35,36} and with recent studies of interactions between *C. albicans* and *P. aeruginosa*, *S. aureus* and others (see ref. 52). We predict that many other interkingdom interactions will be identified with direct relevance to human health and a fascinating underlying biology.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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