

PEARLS

Interplay between host and *Candida albicans* during commensal gut colonizationAndrew W. Day^{1,2}, Carol A. Kumamoto^{2*}**1** Graduate School of Biomedical Sciences, Tufts University, Boston, Massachusetts, United States of America, **2** Department of Molecular Biology and Microbiology, Tufts University, Boston, Massachusetts, United States of America* carol.kumamoto@tufts.edu**Introduction**

Mammals are naturally colonized with a diverse consortium of microbes composed of bacteria, fungi and other organisms. Although fungi make up a small percentage of the total microbial community, they have significant effects on the gastrointestinal ecosystem. For example, the presence of fungal species in the gut community affects the host immune system [1]. The bacterial community is affected by the presence of fungi and the response of the bacterial community to antibiotic stress is altered when a fungus is introduced. Additionally, fungi affect gut metabolite levels with impacts on the physiology of the host. In this communication, we will discuss some of the ways that the fungus *Candida albicans* interacts with its host, including the beneficial effects of *C. albicans* against disease due to *Clostridioides difficile* infection. We also consider the effects of *C. albicans* colonization on the gut–brain axis.

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Gut colonizing fungal populations are the sources of organisms that cause invasive fungal infection

Many fungal pathogens such as the primary pathogens *Coccidioides immitis*, *Histoplasma capsulatum*, and *Blastomyces dermatitidis* and the opportunistic pathogens *Cryptococcus neoformans* or *Aspergillus fumigatus* are environmental. These organisms often initiate infection in the lungs after they are inhaled by the host.

On the contrary, *C. albicans* does not have a major environmental reservoir and can be acquired by human infants early in life [2], probably from caregivers. *C. albicans* is thought to colonize its host as a normal member of the human gut microbiome for long periods of time without causing disease. If the host becomes immunocompromised, colonizing *C. albicans* can disseminate from the gut and cause potentially life-threatening candidiasis [3]. Invasive candidiasis is usually caused by endogenous organisms [4].

Gene expression in colonizing *C. albicans* is regulated so that fungal behavior responds to and influences host immune status

During experimental murine colonization, gene expression in *C. albicans* cells was found to differ depending on the immune status of the host [5]. Expression of *EFG1*, encoding a key transcription factor that regulates many important activities of *C. albicans*, was higher during colonization of healthy mice (BALB/c) and lower during colonization of immunodeficient mice (*nu/nu* BALB/c). Under experimental conditions, immunodeficient mice showed no evidence of disease but the colonizing fungi responded to their immunodeficiency by expressing lower levels of *EFG1*.

The mechanism for coupling gene expression in colonizing fungi to the status of the host's immune response rests on natural variability in *EFG1* expression from cell to cell and the properties of low Efg1 activity cells [5,6]. These cells can be considered “testers” of the host's immune status. Changes in *EFG1* expression probably occur early during the transition of a host from an immunocompetent to immunosuppressed state and may herald the change in the fungal population from benign commensals to invasive pathogens.

Variation in expression of another *C. albicans* transcription factor, Ume6, during commensal colonization promotes the protective Th17 response of the host [7] providing additional evidence that variability in *C. albicans* gene expression impacts the interaction between *C. albicans* and the host. These examples illustrate the nuanced interactions between host and *C. albicans* that allow each to respond to changes in the other.

***C. albicans* gut colonization alters susceptibility to bacterial infection**

Since the status of the host affects *C. albicans* gene expression and variation in gene expression alters interaction with the host, it seemed possible that *C. albicans* colonization could have far-reaching effects on host physiology. Here, we will discuss effects of colonization on host susceptibility to gastrointestinal infection and on the gut–brain axis.

Several studies show that *C. albicans* and bacteria affect each other's virulence. For example, we analyzed the effect of pre-colonization with *C. albicans* on the susceptibility of mice to *Clostridioides* (formerly *Clostridium*) *difficile* infection and demonstrated a protective effect of pre-colonization against this important infection. *C. difficile* infection (CDI) is the most common nosocomial infection in the United States and is responsible for considerable morbidity and mortality. We asked whether the presence of *C. albicans* in the gut community would alter the course of CDI. Results showed that the presence of *C. albicans* was protective against lethal CDI in mice [8].

C. albicans pre-colonization was associated with changes in the host GI tract. Stronger expression of the protective cytokine IL-17A was detected in *C. albicans* pre-colonized mice [8]. Additionally, changes in the gut metabolome associated with *C. albicans* colonization affected disease severity [9]. Specifically, elevated levels of unsaturated fatty acids were observed in *C. albicans* colonized mice and feeding mice without *C. albicans* a source of unsaturated fatty acids (olive oil) was protective against lethal CDI. Further, *C. difficile* cultured in laboratory media containing oleic acid (the major fatty acid constituent of olive oil) grew but with reduced expression of toxin genes. Also, *C. difficile* cells recovered from the cecal epithelium of olive oil-fed mice exhibited reduced toxin gene expression. The results thus show that *C. albicans* colonization changed the gut metabolite environment in a way that reduced *C. difficile* virulence.

C. albicans is not the only organism that is protective against *C. difficile* infection. Commensal bacteria such as *Clostridium scindens* [10], Lachnospiraceae [11], and *Paraclostridium bifermentans* [12] are also protective against murine CDI. The mechanisms involved in protection differ, but these results show that multiple commensal organisms can protect against this bacterial infection.

C. albicans shows interaction with other bacterial species. Pre-colonization with *C. albicans* reduced the virulence of *Pseudomonas aeruginosa* following oral inoculation of neutropenic mice [13]. In contrast, some combinations of *C. albicans* and bacteria have the opposite effect and increase virulence [14–16]. Additionally, some bacteria such as *Enterococcus* and *Pseudomonas* express antifungal activities [17,18]. These findings demonstrate that *C. albicans*–bacterial interactions affect virulence in multiple ways and are consequential for the host.

***C. albicans* colonization affects the gut–brain axis**

Impacts of the gut microbiota on the brain through the gut–brain axis have recently become the subject of investigation. The gut–brain axis is defined as the bidirectional communication between the brain and the gastrointestinal tract through direct and indirect pathways including direct neuronal innervation of the intestines, metabolic pathways, and immune system modulation. All of these pathways can be impacted by gastrointestinal microbes or microbial products and can impact activities in the brain.

Gastrointestinal colonization by *C. albicans* resulted in altered behavior in mice [19]. Mice colonized with *C. albicans* had elevated afternoon corticosterone and an anxiety-like phenotype due to dysregulation of lipid metabolism and perturbation of the endocannabinoid system [19]. Endocannabinoids are signaling lipids that regulate synaptic transmission and modulate inflammation, neurological development, memory formation, anxiety, and depression [20]. Based on the functions of the endocannabinoid system, it is likely that *C. albicans* or other microbes that alter the endocannabinoid system would have other behavioral impacts. In fact, in a chronic unpredictable stress model, microbiota dysbiosis and endocannabinoid perturbations contributed to the development of depressive-like behavior [21].

Furthermore, *C. albicans* affects other pathways such as immune responses that could modulate neuroinflammation. Additionally, *C. albicans* impacts plasma levels of ketones such as β -hydroxybutyrate [22], a lipid molecule that has neuroprotective effects. β -hydroxybutyrate was reduced in mice colonized with microbiomes from humans with alcohol use disorder [23] and this reduction correlated with depression-like behavior and altered social behavior in these mice.

In summary, the gut–brain axis is extremely complex. Many different microorganisms are involved in its modulation through a number of pathways, leading to a variety of microbiota-responsive neuropsychological phenotypes.

Possible contributions of *C. albicans* and gut microbiota to the evolutionary fitness of the host

Why does *C. albicans* have such profound effects on its host? As discussed above, *C. albicans* is not the only organism to affect susceptibility to bacterial infection or signaling in the gut–brain axis. Other members of the gut microbiota have similar effects. These observations suggest that the impacts of microbiota on the host could represent an important way to generate diversity in a human population. Microbiota diversity could protect the population as a whole from extinction due to endemic or invasive pathogens that would otherwise cause widespread mortality in a genetically similar population. Additionally, variability in microbiota composition between humans could have very individual effects on each person's gut–brain axis. As a result, each person's response to a stressful condition could be slightly different. Diversity in responses to danger may promote survival of a group by increasing the chances that the group will find an optimal response. In small family groups where genetic diversity may not be high, microbiota diversity may provide a needed mechanism that allows the group to sample a wider variety of responses to danger. The microbiota–gut–brain axis thus provides survival benefits in a cruel world.

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Author Contributions

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