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Current Opinion in Microbiology

Candida albicans dwelling in the mammalian gut

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The yeast *Candida albicans* inhabits the gastrointestinal tract of most healthy adults, seemingly living there as a harmless commensal. The fungus on occasion disseminates from the gut to other internal organs causing life-threatening infections. Here, I review some of the most exciting advances in the study of gut colonization by *C. albicans* in the last few years. These developments highlight the close interplay between *C. albicans* and cohabiting microbes, the responses that commensal fungi elicit from the mammalian host, and the genetic determinants that allow the fungus to thrive in such a crowded and demanding ecosystem.

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Current Opinion in Microbiology 2019, **52**:41–46

This review comes from a themed issue on **Host-microbe interactions: fungi**

Edited by **Chad A Rappleye** and **Duncan Wilson**

For a complete overview see the Issue and the Editorial

Available online 25th May 2019

https://doi.org/10.1016/j.mib.2019.04.007

The human intestine harbors a large variety of non-bacterial microbes [1–3]. Research on the non-bacterial microbiota, however, has lagged behind compared to studies looking at the prokaryotic component. Fortunately, there is now a growing interest in exploring the role that non-bacterial microorganisms have in the gut ecosystem and how these microbes contribute to health and disease [4,5]. The ascomycete yeast *Candida albicans* [6] is the most prominent fungus residing in the human gut. Thus, a natural endeavor would have been to investigate the biology of this eukaryotic microbe in the gastrointestinal tract. Historically, however, the vast majority of studies on *C. albicans* have focused on traits thought to directly contribute to mucosal or bloodstream infections, leaving many aspects of intestinal colonization underexplored. Luckily, the sparse knowledge on the biology of *C. albicans* in the gut is now being filled at steady pace, driven to a large extent by efforts in functional genomics [7].

In addition to being a human commensal, *C. albicans* is the major cause of serious fungal infections: It can disseminate from the gut into the bloodstream and colonize almost every internal organ producing deep-seated, life-threatening infections. Because *C. albicans* resides in the gastrointestinal tract along with hundreds of other microbial taxa, it is plausible that the intestinal flora directly influences *C. albicans* proliferation as either commensal or pathogen. Consistent with this notion, it has been observed for a long time that antibiotic treatment in humans results in *Candida*'s overgrowth [8,9], presumably due to the dampening of competing microbes. Therefore, studying the biology of *C. albicans* in the gut, in particular the interplay with other microbes, may allow researchers to devise interventions aimed at preventing *Candida* systemic infections that originate in the gastrointestinal tract.

Experimental systems to study the biology of *C. albicans* in the mammalian intestine

Although mice are not the natural hosts of *C. albicans*, these animals have been instrumental in dissecting how the fungus causes disease in humans [10]. Rodents are now also being used to investigate traits associated with *C. albicans* commensal colonization of the gastrointestinal tract [11]. Adult mice with mature intact microbiota are resistant to *C. albicans* intestinal colonization [12–14]. For that reason, murine gut colonization with this fungus is routinely achieved by the non-selective reduction of the mouse indigenous flora through antibiotic treatment [11,13,15–17]. Yet a significant amount of indigenous flora — particularly anaerobes — still persists while administering antibiotics [12]. Whether this residual and undefined microbiota impacts on the biology of *C. albicans* is unknown.

Dissecting the *C. albicans*-host interplay in the murine intestine might be confounded by cryptic effects arising from leftover microbes after antibiotic treatment. Gnotobiotic mice provide an alternative to circumvent such limitation. In this experimental system, *C. albicans* is administered orally to animals that have been raised in a microbe-free environment (germ-free mice). Reports from the 1960s and early 1970s already described the feasibility of establishing long-term *C. albicans* colonization in the gut of various strains of germ-free mice [18,19]. Consistent with these early studies, it has recently been shown that this fungus can successfully colonize the gastrointestinal tract of germ-free rodents for at least

three weeks after a single gavage with no overt effects on the health of the animals [20•].

Genetic determinants of *C. albicans* fitness in the gut

C. albicans has virtually no known natural reservoir outside the host, implying that fungus and host have co-evolved to establish a predominantly symbiotic relationship. It has been of interest, therefore, to identify the *C. albicans* genetic determinants that enable the fungus to inhabit the mammalian intestine. Although a handful of genes with roles in murine gut colonization had been spotted [17,21,22], the first relatively unbiased and systematic search for *C. albicans* gut colonization genes was reported in 2013 [16]. These first studies employed the standard antibiotic-treated mouse model of intestinal colonization. More recently, a similar genetic screen was conducted in gnotobiotic mice monocolonized with *C. albicans* (i.e. germ-free animals gavaged with the fungus) [20•]. These rather complementary approaches are revealing gripping details on various facets of the organism's biology (Table 1).

One aspect is the importance of the morphology that *C. albicans* adopts. The fungus is known to alternate among multiple morphologies, the most common of which are the oval-shaped 'yeast' form, the filaments (hyphae or pseudohyphae) and the somewhat elongated 'opaque' cells [23]. These forms massively differ from one another in their gene expression profiles, metabolic properties, surface molecules and overall function. It is also well established that the ability to switch between morphologies, particularly the yeast-to-hyphae transition, is critical during pathogenesis. In the mammalian intestine, however, maintaining the yeast form appears paramount (Figure 1) (although an alternative morphology called GUT phenotype has been postulated as particularly adapted to the digestive tract [15]). Several findings support the importance of the yeast form: First, independent studies have found that deletion of either *EFG1* or *FLO8*, two well-studied regulators that promote filamentation, increases the fitness of *C. abicans* in the gut of antibiotic treated-mice [21,24•]; second, ectopic expression of *UME6*, a driver of yeast-to-filament transition, impairs colonization [20•]; third, the genes *ZCF8*, *TRY4* and *ZFU2*, which were recently shown to be necessary for *C. albicans* to persist in the gut of gnotobiotic animals, are negative regulators of filamentation [20•]; fourth, null mutations in *HMS1* and *CPH2*, two related genes that promote the yeast morphology under anaerobic conditions [25], cause impaired colonization [16,22]; and fifth, the yeast morphology was the most abundant form detected in the colon of gnotobiotic mice monocolonized with the fungus [20•]. While the yeast form appears fitter in the intestine, other morphologies may be better suited to thrive in other mucosae. For example, filaments are clearly prominent in the oral mucosa [26] and this does not necessarily equate to pathogenesis [26,27]. The evolutionary pressure for *C. albicans* to maintain the ability to switch between morphologies may arise in this dichotomy.

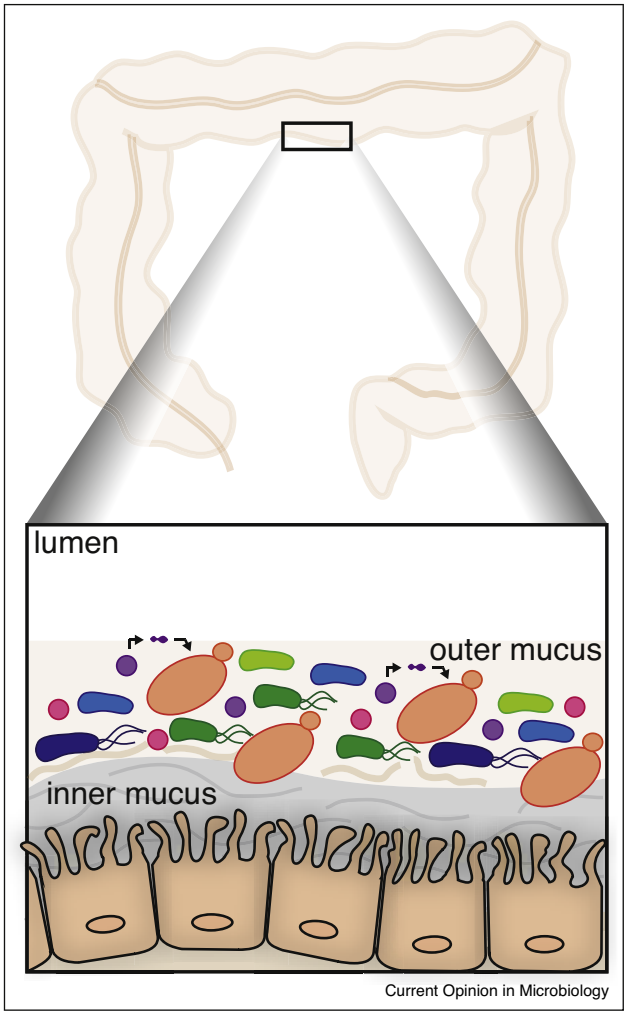
A second aspect is the regulation of metabolic and cell wall functions as significant contributors to fitness in the

Table 1

***C. albicans* genes with roles in gut colonization**

Biological process	Systematic name	Standard name	Known or predicted function	Reference
Yeast-to-filament transition	CR_07890W_A	*EFG1*	Transcription regulator	[21]
	C2_06340W_A	*EFH1*	Transcription regulator	[17]
	C6_00280W_A	*CPH2*	Transcription regulator	[22,25]
	C5_00670C_A	*HMS1*	Transcription regulator	[16,20•,25]
	C3_05050W_A	*TRY4*	Transcription regulator	[20•]
	C3_01330W_A	*ZCF8*	Transcription regulator	[20•]
	C3_07200C_A	*ZFU2*	Transcription regulator	[20•]
	C6_04350C_A	*FLO8*	Transcription regulator	[24•]
	C3_01800C_A	*DIG1*	Transcription factor regulator	[58]
	C7_00360W_A	*DFI1*	Cell-surface protein	[16,57]
Iron homeostasis	C1_10020W_A	*SFU1*	Transcription regulator	[32]
White-to-opaque switch	C1_10150W_A	*WOR1*	Transcription regulator	[15]
Peptide toxin	C4_03470C_A	*ECE1*	Cytolytic peptide toxin	[17]
Metabolism	C2_00680C_A	*SOD5*	Superoxide dismutase	[33]
	C1_13140C_A	*TYE7*	Transcription regulator	[16,20•]
	C1_08640W_A	*RTG1*	Transcription regulator	[16,20•]
	C1_10990C_A	*RTG3*	Transcription regulator	[16,20•]
	C3_00750W_A	*LYS144*	Transcription regulator	[16]
Stress response	C2_03330C_A	*HOG1*	Kinase	[30]
Cell wall	CR_07060C_A	*CRZ2*	Transcription regulator	[28•]
	CR_00120C_A	*MKC1*	Kinase	[30]
	C4_06480C_A	*CEK1*	Kinase	[30]

Figure 1



The yeast *C. albicans* in the mammalian intestine.
Cartoon depicting an idealized scenario of the mammalian colon where *C. albicans* cells have been imaged (see Ref. [20•]). In this niche, the oval 'yeast' form of the fungus may be prevalent. Fungal cells (in orange) are expected to occupy the loose outer mucus layer together with cohabiting bacteria (depicted in various colors and shapes). Other gut microbes likely produce molecules that directly or indirectly impact on *C. albicans* traits. Illustrated is a documented case in which a peptide toxin secreted by *E. faecalis* (in purple) directly acts on *C. albicans* (see Ref. [43•]).

mammalian intestine. The *C. albicans* regulator *CRZ2* illustrates this point well. Znaidi *et al.* [28•] identified *CRZ2* as a determinant of early settlement in the gut by conducting a high-throughput screen of ca. 500 conditional overexpression strains. Combining genome-wide molecular biology approaches, the authors established that Crz2p governs the expression of genes linked to cell wall function and carbohydrate metabolism. Consistent with its role in gut colonization, Crz2p activity was optimal under hypoxia at 37°C. The importance of carbohydrate metabolism is further supported by the finding that *TYE7*, a major regulator of glycolytic genes [29], was also necessary for intestinal colonization [16]. *C. albicans* strains harboring null mutations in the kinases *MKC1*, *CEK1*, and *HOG1*, all of which are involved to some extent in the biogenesis and maintenance of the cell wall, also exhibit reduced fitness in murine gut colonization [30]. Bacteria that inhabit the mammalian gut are known to dedicate plenty of assets to secure carbon sources [31]; hence, the involvement of *C. albicans* sugar metabolism regulators in gut colonization may be indicative of an analogous trait in this fungus. On the other hand, the context in which cell wall modifications influence *C. albicans* fitness in this niche — for example, during interactions with host defense mechanisms or with cohabiting microbes — remains to be established.

Other biological functions such as managing iron toxicity [32] and detoxification of reactive oxygen species [33] also contribute to *C. albicans* colonization of the gastrointestinal tract and have been reviewed elsewhere [11]. An intriguing factor that is worth mentioning because it has received much attention lately is *ECE1*. This gene encodes a product that is later processed to smaller peptides, one of which is the cytolytic peptide toxin Candidalysin [34]. This peptide toxin is essential for the fungus to damage epithelial cells including keratinocytes [34] and enterocytes [35]. While this activity explains its role in mucosal pathogenesis, the reduced fitness of the *ece1* deletion mutant in murine gut colonization [17] is not straightforward to rationalize. The observation that *ECE1* had a role in intestinal colonization was made long before the gene was linked to Candidalysin. Whether the same peptide toxin mediates this phenotype (several distinct products are made from the primary peptide encoded by *ECE1*) and whether the mechanism(s) involve(s) targeting a host function or other microbes has yet to be elucidated.

Gut bacteria — *C. albicans* interplay

Fungal and bacterial populations not only coexist in the mammalian intestine but also exert influence on each other (Figure 1). For example, mice treated with antifungal drugs exhibit pronounced alterations in the composition of their bacterial flora [36]. *C. albicans* itself has been shown to impact the reassembly of gut bacterial communities after antibiotic treatment [37,38] and is associated with reduced efficacy in fecal transplants currently in use to treat recurrent *Clostridium difficile* infections [39]. Unfortunately, the mechanisms underlying these observations are unclear. In fact, one of few cases in which the basis of an antagonistic relationship between *C. albicans* and bacterial species is known — in a murine model of intestinal colonization — was reported by Fan *et al.* [12]. The authors found that several Bacteroidetes and clostridial Firmicutes antagonize *C. albicans* in the murine intestine. These bacteria limited proliferation of the fungus by stimulating the production of gut mucosal immune defenses against *C. albicans*.

Potential interactions between single bacterial species and *C. albicans* have more often been studied in the context of *in vitro* biofilm formation. It has been observed that, in this context, the gram-positive bacterial pathogens *Staphylococcus aureus* and *Clostridium perfringens*, the commensal *Enterococcus faecalis*, and the gram-negative bacteria *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa* and *Bacteroides fragilis* can physically associate with *C. albicans* cells [40–42]. A secreted bacteriocin by *E. faecalis* has even been shown to inhibit the formation of *C. albicans* filaments, preventing biofilm formation [43•] (Figure 1). While some of these multi-species biofilms do occur in intravascular catheter-related infections [44], it remains to be determined whether these species indeed physically interact with one another when growing in the host in their natural niche. The clinical observation that mixed infections consisting of *C. albicans* and the bacterial pathogen *P. aeruginosa* frequently occur in chronic lung infections and in association with contaminated plastic medical devises has prompted a more in-depth examination of *P. aeruginosa–Candida* interactions [45]. These studies have revealed that, when grown together *in vitro*, *P. aeruginosa* secretes molecules that modulate *C. albicans* metabolism, morphology and growth, suggesting an antagonistic relationship [46–48]. A study in a murine model of intestinal colonization, however, found that co-colonization had no effect on *C. albicans* or *P. aeruginosa*'s individual ability to colonize this niche [49]. Thus, the physiological relevance of many of the *in vitro* observations remains to be established. As the field moves forward, it is evident the need to incorporate well-defined mammalian model systems to investigate the synergistic, symbiotic or antagonistic interactions between fungi and bacteria.

C. albicans and immune responses in the gut

Fungal members of the intestinal community have been shown to influence the immunological responses of the host by dampening or promoting local inflammatory responses [36,50]. *C. albicans*, for instance, is thought to exacerbate inflammatory processes due to a sequence of events that perpetuate on each other: Low-level inflammation in the intestine fuels the expansion of the fungus while *C. albicans* overgrowth promotes further inflammation (reviewed in Ref. [51]). This process could explain, at least in part, the link between the fungus and inflammatory bowel disease, for example, ulcerative colitis and Crohn's disease. More recently, it has been established that commensal fungi such as *C. albicans* play conspicuous immune modulatory roles in protecting against disease locally in the intestine but also systemically in extra-intestinal tissues [24•,52••]. Jiang *et al.* [52••] found that *C. albicans* monocolonization efficiently overturned the fatal susceptibility to influenza A virus infection among commensal-bacteria-depleted mice. The authors further demonstrated that similar protective effects were obtained by simply administering mannans, a major cell wall component of the fungus, and that TLR4 was necessary for the mice to receive the protection.

Tso *et al.* [24•] have also reported that priming mice with *C. albicans* strains — although in this case the strains employed had been passaged multiple times through the gut of mice to improve the fungus' fitness — led to cross protection against multiple fungal and bacterial pathogens. This effect was considered a case of 'trained immunity' [53,54] because it was rapidly established, independent of adaptive immunity, relatively short lived and required cytokine production [55]. By contrast, the finding described in the previous paragraph regarding protection conferred by *C. albicans* monocolonization to commensal-bacteria-depleted mice [52••] seems to be at odds with the concept of 'trained immunity'. Jiang *et al.* [52••] showed that the systemic immune modulation effects depended on the tonic presence of commensal fungi. 'Trained immunity', in contrast, is primed by invasive fungi and is triggered by the sensing of pathogens in sterile tissues after parental injection [53].

Independently of the mechanism, the described studies underscore the notion that commensal fungi such as *C. albicans* elicit consequential and diverse responses from the gastrointestinal tract. In fact, specific immune cells residing in the intestine — the mononuclear phagocytes expressing the fractalkine receptor CX3CR1 — have recently been shown to be essential for the initiation of immune responses elicited by *C. albicans* and other intestinal fungi [56••].

Conclusions

In the last few years, there has been an increasing interest in exploring the interplay between commensal fungi such as *C. albicans*, cohabiting bacteria and the mammalian intestine. These studies are revealing multiple biological functions that are critical for *C. albicans* to inhabit the gastrointestinal tract. Some of the identified functions highlight common challenges faced by bacterial and eukaryotic (e.g. fungal) species when colonizing this particular niche. The findings also provide evidence of potentially noteworthy interkingdom (fungi-bacteria) interactions taking place between *C. albicans* and intestinal bacteria. Furthermore, we are learning about the local and systemic immune responses that *C. albicans* and other commensal fungi elicit from the gut. Clearly, we are at the beginning of an exciting journey that is likely to deliver significant insights into how non-bacterial members of our microbiota contribute to human health and disease.

Conflict of interest statement

Nothing declared.

Acknowledgements

I thank Lena Boehm for the artwork and Elena Lindemann for reading and providing valuable comments on the manuscript. *C. albicans* work in the

Pérez lab is supported by funding from the Deutsche Forschungsgemeinschaft (DFG) (projects PE 2371/2-1, PE 2371/3-1 and TRR 124 FungiNet C01) and the Interdisziplinäres Zentrum für Klinische Forschung der Universität Würzburg (project A-296).

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