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Inflammation and gastrointestinal *Candida* colonization

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SUMMARY

Candida organisms commonly colonize the human gastrointestinal tract as a component of the resident microbiota. Their presence is generally benign. Recent studies, however, show that high level *Candida* colonization is associated with several diseases of the gastrointestinal tract. Further, results from animal models argue that *Candida* colonization delays healing of inflammatory lesions and that inflammation promotes colonization. These effects may create a vicious cycle in which low-level inflammation promotes fungal colonization and fungal colonization promotes further inflammation. Both inflammatory bowel disease and gastrointestinal *Candida* colonization are associated with elevated levels of the pro-inflammatory cytokine IL-17. Therefore, effects on IL-17 levels may underlie the ability of *Candida* colonization to enhance inflammation. Because *Candida* is a frequent colonizer, these effects have the potential to impact many people.

Introduction

Colonization of the human gastrointestinal (GI) tract by opportunistic fungal pathogens such as *Candida albicans* is significant because *C. albicans* infections are believed to arise from commensal organisms [1,2]. In a recent study that supports this view, Miranda et al [3] recovered *Candida* organisms from the blood of patients with candidiasis and compared those organisms to organisms cultured from the rectum or skin of the same patient. In most cases of *C. albicans* candidemia, the strain identified in a patient's blood sample and the strain identified in the same patient's rectum sample were identical. These findings support the model that commensal organisms residing in the GI tract can escape from this niche and reach the bloodstream. Interestingly, in the same study, *Candida parapsilosis* blood stream isolates did not correspond to isolates detected in rectum or oral samples [3]. Most of these cases of *C. parapsilosis* candidemia were catheter-associated infections in neonates. As previously noted [1], these types of infections have a different origin and generally do not arise from gut flora.

In addition to its relevance as the reservoir for disease-causing organisms, the GI tract is an important niche in the lifecycle of *C. albicans* because this organism does not have a significant environmental reservoir. Rather, *C. albicans* is almost always found associated with humans or other mammals, typically in the GI tract, genitourinary tract or on skin [2,4]. In the GI tract, *C. albicans* encounters and responds to varying features of the physical

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environment such as pH, oxygen levels and nutrient levels [5]. *C. albicans* also responds to secretions produced in the GI tract such as bile [6]. These findings argue that *C. albicans* is well adapted for growth in the GI tract.

Analyses of factors that regulate *C. albicans* colonization show that the host immune system (e.g. [7–14]), bacterial competitors [7,15–19], and fungal gene expression [5,17,20–23] impact GI tract colonization by the organism. Colonization levels thus reflect an interplay between host activities, bacterial activities and fungal activities.

The remainder of this review will focus on the effects that *Candida* colonizing the mammalian GI tract exerts on its host. In mice, *C. abicans* colonization of the stomach results in expansion of regulatory T cell populations [24] and regulatory T cells are associated with immunosuppressive effects on the host. However, in a setting of inflammation, *Candida* colonization appears to exacerbate inflammation. Several recent studies will be reviewed below.

Candida colonization is associated with diseases of the GI tract

Candida colonization in patients suffering from GI tract disease has been documented in several situations. As shown in Table 1, patients with different diseases affecting the GI tract were colonized with *Candida* more frequently than control individuals.

Crohn's disease

The inflammation that is characteristic of Crohn's disease (CD), a type of inflammatory bowel disease (IBD), is thought to arise as a result of dysregulated immune interactions between the host and components of the intestinal microbial flora. To test for an association between *Candida* colonization and CD, a large-scale study of families in which multiple members suffered from CD was conducted [25]. The authors studied both CD patients and their unaffected, healthy relatives (HR). Healthy relatives often exhibit characteristics that have been noted in patients such as increased intestinal permeability or defects in oral tolerance [26–32], but they do not have clinical disease. HRs are therefore less likely to have been treated with medications that might increase the likelihood of *Candida* colonization, such as antibiotics and immunomodulators.

Stool samples from both patients (Table 1) and HR more frequently contained significant levels of *C. albicans* than stool samples from control individuals, individuals who lived in the same geographic region and had no history of IBD [25]. In addition to increased frequency of colonization, patients and HR carried *C. albicans* at higher levels than control individuals. A similarity in colonization between patients and HR was observed when family members lived together in the same household and when they did not. Therefore, similarity in carriage within families was not simply due to a shared environment. The authors suggest that subclinical inflammation is present in HRs; this effect could influence *C. albicans* colonization. Thus, this study demonstrated an association between familial Crohn's disease and intestinal colonization by *C. albicans*.

Ulcerative colitis

Patients with ulcerative colitis (UC), another form of IBD, are also frequently colonized by *Candida* [33,34]. For example, in one study, many patients with long standing disease (duration >5 yr) had high level colonization detected in stool or brush smears from inflamed mucosa (Table 1)[34]. Among the control group, individuals with diarrhea but not UC, only one person was highly colonized (Table 1). Further, in patients with active disease who were colonized with *Candida*, treatment with the antifungal drug fluconazole led to a reduction in

clinical signs and in the size of inflammatory lesions. Although these effects may be direct or indirect, the results argue that reducing *Candida* colonization reduced disease severity.

Gastric ulcers

Candida organisms colonize ulcers, particularly when the ulcers are large or perforated (Table 1). In several studies, *Candida* organisms were cultured from gastric biopsies, brush samples of mucosa or peritoneal fluid. Colonization was observed more frequently in older patients [35,36] and in patients with hypoacidity [36]. In addition, the rate of decrease in ulcer diameter, an indication of ulcer healing, was slower in patients whose stomachs were significantly colonized by *Candida* in comparison to patients who were not [37]. These studies of UC patients and gastric ulcer patients show that significant colonization with *Candida* is associated with more severe disease.

To summarize, higher level colonization by *Candida* was associated with several diseases of the GI tract. Although some of the studies are small and lack sufficient numbers of controls, the results of several studies reinforce each other and support the overall conclusion.

C. albicans colonization inhibits the healing of inflammatory lesions in animal models

To elucidate the interplay between *Candida* and the host during disease, animal models of GI tract disease have been employed. For studies of ulcers, rats or mice are treated with ulcer inducing chemicals such as cysteamine, a compound that concentrates in the duodenum producing duodenal ulcers [38].

When rats received cysteamine treatment and *C. albicans* inoculation on the same day, almost all rats (16/17) developed perforated duodenal ulcers [38]. Rats who received cysteamine but no *Candida* exhibited perforated ulcers at a lower frequency (4/15; $p<0.01$). The area and depth of the ulcers were also greater in the presence of *C. albicans* than in its absence. Rats receiving *C. albicans* alone without cysteamine did not develop ulcers. Therefore, in this model, ulcers were more severe when *C. albicans* was present.

In a subsequent study, *C. albicans* was administered to rats beginning 3 days after cysteamine treatment [39]. The duodenum of these rats was examined several days later, when ulcer healing should have begun. Duodenal ulcers were observed in 70% of the rats treated with both cysteamine and *C. albicans* compared to 33% of rats that received only cysteamine ($p<0.05$). The area of the ulcers was significantly larger in the animals that received both cysteamine and *C. albicans*. Ulcer scarring was observed in animals that did not receive *C. albicans*, but rarely in animals that received *C. albicans*. Therefore, the presence of *C. albicans* delayed ulcer healing in this animal model.

A study of gastric ulcers induced by treatment with acetic acid showed similar effects [40]. Mice that received *C. albicans* exhibited less ulcer healing at day 25 in comparison with mice that did not receive *C. albicans*. Collectively, these results indicate that *C. albicans* colonization increases the severity of ulcers and inhibits their healing.

IBD has been modeled by treating animals with chemicals or by using mutant strains of mice. For example, dextran sulfate sodium (DSS), which injures epithelial cells and causes inflammation, or trinitrobenzene sulfonic acid (TNBS), which produces ulceration, have been used to produce colitis.

Poulain and coworkers treated mice with DSS and some mice were also inoculated with *C. albicans* by oral gavage [41]. The presence of *C. albicans* led to a modest increase in disease

severity. For example, in the presence of *C. albicans*, the mice exhibited severe inflammation with massive influx of neutrophils and tissue destruction. Tissue levels of myeloperoxidase (MPO), indicative of neutrophils in the tissue, were elevated in mice that received *C. albicans* compared to those who did not. Tissue expression of the cytokine TNF-α was also higher in DSS-treated mice that received *C. albicans*.

TNBS-treated rats inoculated with *C. albicans* exhibited a larger area of colonic damage, and increased MPO activity in colon tissue [34]. When fluconazole was administered to the rats along with *C. albicans*, the damage and MPO activity were reduced. Thus, the presence of *C. albicans* enhanced colitis in these animal models. Taken together, these studies show that *C. albicans* exacerbates damage and delays healing of inflammatory lesions in animal models.

Inflammation promotes *C. albicans* colonization of the GI tract

Interestingly, Jawhara et al showed that following oral gavage, *C. albicans* could successfully colonize the GI tract of mice treated with DSS while mice not treated with DSS were not colonized [41]. With conventionally reared mice, *C. albicans* usually fails to colonize the GI tract unless the mice are treated with antibiotics, e.g. [7,15–19]. Therefore, like antibiotic treatment, GI tract inflammation may perturb the resident bacterial community, allowing *C. albicans* to colonize.

The strategy of taking advantage of the effects of inflammation to promote colonization is used effectively by bacterial pathogens. For example, the presence of the enteric pathogen *Salmonella typhimurium* causes inflammation and modifies the resident microbiota; these effects promote *S. typhimurium* colonization [42]. A mutant strain of *S. typhimurium* that fails to provoke inflammation and modify the microbiota is defective in colonizing. Enhancement of colonization through alteration of the microbiota thus represents a successful strategy for establishing colonization in the intestine.

C. albicans does not appear to evoke sufficient levels of inflammation to colonize the mouse GI tract successfully without antibiotic treatment. However, the organism is able to exploit inflammation stimulated through other mechanisms to enhance its ability to colonize.

Since inflammation increases the likelihood of significant *Candida* colonization and *Candida* colonization reduces healing of lesions, these effects would produce a vicious cycle. The presence of inflammation alters bacterial colonization and the activities of the host, creating conditions that favor both high level *Candida* colonization and exacerbation of disease.

Does high-level *C. albicans* colonization trigger IBD?

CD patients and HRs share many characteristics, such as increased intestinal permeability or defects in oral tolerance [26–32], yet HRs do not have disease. To date, no single factor that explains why some people develop CD and others do not has been identified. It is clear that development of CD requires the microbiota. In human patients surgically treated for CD, recurrence of the disease was not observed when the fecal stream was diverted but recurred after fecal transit was restored [43]. In laboratory studies, mice that are genetically susceptible to colitis but are germ free do not develop colitis [44]. Upon colonization with bacterial flora, these mice develop disease. Thus, it is thought that in CD patients, homeostasis between the normal intestinal flora and the host has somehow broken down so that components of the commensal flora evoke an aberrant immune response [45].

It is most likely that some individuals are highly susceptible to CD because of a combination of genetic and environmental factors. In these individuals, one or more triggering event(s) occur that can result in the development of CD. Once the triggering event occurs, immune responses that culminate in recurrent inflammatory conditions are set in motion.

The nature of the putative triggering events is not known. One possible triggering event may be antibiotic use. Analysis of a large database of patient records showed a statistically significant association between antibiotic use, especially tetracycline use, and subsequent diagnosis with CD [46]. Antibiotic use may alter both the total level of bacteria colonizing the intestinal tract and the composition of organisms. Antibiotic use also results in increased *Candida* colonization. Because different organisms differ in their propensity to lead to inflammation [45], these effects of antibiotics may influence the amount or type of stimulation that the immune system receives and affect inflammation.

Recently, attention has focused on the role of a subset of T-helper cells, Th17 cells, in IBD (recently reviewed in [47–51]. Biopsies of inflamed mucosa or blood cells from IBD patients produce higher levels of IL-17, a cytokine secreted by Th17 cells [52–55]. Increased levels of IL-17 are also produced by gastric ulcer biopsies in comparison to non-ulcer tissue [56]. Further, IL-23, a cytokine that promotes the expansion and maintenance of Th17 cells, is required for induction of T-cell mediated colitis in murine models [57–59]. These findings favor a role for IL-23 and IL-17 in IBD.

Intriguingly, colonization by *C. albicans* increases IL-17 and IL-23 production by murine gastric and oral tissues [14,60,61]. Therefore, *Candida* colonization could enhance inflammation by increasing levels of these cytokines. High-level colonization by *Candida* occurring in a susceptible individual with subclinical inflammation could thus exacerbate inflammation and trigger CD, a possibility discussed by Standaert-Vitse et al [25]. Further studies will be required to investigate this possibility.

Concluding remarks

As the studies discussed above show, high-level *Candida* colonization is frequently observed in ulcer and IBD patients. Frequent colonization may, in part, reflect modern treatments for these conditions, which include administration of drugs such as antibiotics or immunomodulators. In addition, the presence of *Candida* delays healing and exacerbates disease. This vicious cycle in which inflammation promotes *Candida* colonization and *Candida* colonization delays healing may impact many patients. The effects of antifungal treatment on UC patients [34] argue that reduction in fungal colonization could be beneficial for colonized patients. Interestingly, administration of the probiotic *Lactobacillus acidophilus* reduced symptoms of UC in human patients [34] and reduced ulcer size in acetic-acid treated rats that received *C. albicans* and an inhibitor of gastric acid secretion [37,40]. These findings suggest that by antagonizing *Candida* colonization, modulation of the bacterial microbiota could provide beneficial effects for patients. Further studies to discern the mechanisms for the effect of inflammation on *Candida* colonization and the effect of *Candida* on inflammatory lesions represent exciting directions for future research.

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HIGHLIGHTS

1. High level colonization with *Candida* is more common in patients with GI tract disease
2. In an animal model, intestinal inflammation promotes *Candida* colonization.
3. Do interactions between inflammation and *Candida* colonization create a vicious cycle?

Table 1

Fungal colonization in patients with GI tract disease

Disease condition	Sample cultured	Patients significantly colonized by *Candida*[a] Number/total (%)	Controls significantly colonized by *Candida*[a] Number/total (%)	p value	Reference
Crohn's disease, familial	Stool	47[b]/107 (43.9%)	13[b]/59 (22%)	<0.05	[25]
Ulcerative colitis (>5 yrs duration)	Stool or brush smear of mucosa	33/47 (70%)	1/12 (8.3%)	0.0005	[34]
Ulcerative colitis	Stool	36/42 (86%)	N.R.	N.A.	[33]
Gastric ulcers	Gastric biopsy or brush smear	51/94 (54.2%)	4/92 (4%)	N.R.	[37]
Duodenal ulcer	Biopsy or brush sample	(large duodenal ulcer) 8/10 (80%)	(small duodenal ulcer) 27/70 (38.6%)	<0.05	[36]
Perforated ulcer	Peritoneal fluid	9/22 (41%)	N.A.	N.A.	[62]
Perforated ulcer peritonitis	Peritoneal fluid	23/62 (37%)	N.A.	N.A.	[63]

[a] Measured by culture

[b] C. albicans

N.R., not reported

N.A., not applicable

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