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REVIEW

Interplay between *Candida albicans* and Lactic Acid Bacteria in the Gastrointestinal Tract: Impact on Colonization Resistance, Microbial Carriage, Opportunistic Infection, and Host Immunity

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SUMMARY Emerging studies have highlighted the disproportionate role of *Candida albicans* in influencing both early community assembly of the bacterial microbiome and dysbiosis during allergic diseases and intestinal inflammation. Nonpathogenic colonization of the human gastrointestinal (GI) tract by *C. albicans* is common, and the role of this single fungal species in modulating bacterial community reassembly after broad-spectrum antibiotics can be readily recapitulated in mouse studies. One of the most notable features of *C. albicans*-associated dysbiotic states is a marked change in the levels of lactic acid bacteria (LAB). *C. albicans* and LAB share metabolic niches throughout the GI tract, and *in vitro* studies have identified various interactions between these microbes. The two predominant LAB affected are *Lactobacillus* species and *Enterococcus* species. Lactobacilli can antagonize enterococci and *C. albicans*, while *Enterococcus faecalis* and *C. albicans* have been reported to exhibit a mutualistic relationship. *E. faecalis* and *C. albicans* are also causative agents of a variety of life-threatening infections, are frequently isolated together from mixed-species infections, and share certain similarities in clinical presentation—most notably their emergence as opportunistic pathogens following disruption of the microbiota. In this review, we discuss and model the mechanisms used by *Lactobacillus* species, *E. faecalis*, and *C. albicans* to modulate each other's growth and virulence in the GI tract. With multidrug-resistant *E. faecalis* and *C. albicans* strains becoming increasingly common in hospital settings, examining the interplay between these three microbes may provide novel insights for enhancing the efficacy of existing antimicrobial therapies.

KEYWORDS *Candida albicans*, enterococcus, gastrointestinal, lactobacillus, lactic acid bacteria, polymicrobial infection

INTRODUCTION

There is increasing evidence that the fungus *Candida albicans* plays a disproportionate role in modulating the microbial ecology of the human gut microbiome and subsequent mucosal immune responses. The intestinal microbiota is a multiplex system that is capable of suppressing indigenous pathogens while modulating essential homeostatic functions, such as digestion and immune responses (1). In a recent longitudinal cohort examination of 178 preterm infants, investigators studied the community dynamics of bacteria, fungi, and archaea in the intestine and reported periods of microbial blooms, microbial extinctions, and an inverse correlation between bacterial and fungal loads (2). Most notably, they discovered that interactions with a single fungal species (*C. albicans*) can influence early microbiome community assembly and inhibit multiple dominant genera of intestinal bacteria. This correlation between *Candida* levels and a dysbiotic microbiota (including diminished *Lactobacillus* levels) has also been reported in an atopic cohort of children (3, 4) and parallels our laboratory's observations in mouse models of antibiotic-mediated dysbiosis and allergic disease (5, 6). Intestinal microbiome-derived *Lactobacillus* strains can antagonize the opportunistic pathogens *Enterococcus faecalis* and *C. albicans*, which are also causative agents of a variety of life-threatening infections and are frequently isolated together from mixed-species infections (7). Studies in which *E. faecalis* and *C. albicans* are sole colonizers of the *Caenorhabditis elegans* gastrointestinal (GI) tract have found that these two microbes promote each other's growth but actually dampen each other's virulence, suggesting a complex mutualistic relationship which is likely further influenced by other organisms in their niche (8, 9). Using mouse models, our laboratory has reported an antagonistic relationship between *C. albicans* and *Lactobacillus johnsonii* and a positive association between *C. albicans* colonization and levels of *E. faecalis* (10–12). These observations, together with others (described in the following sections), provide evidence that *C. albicans* can play a significant role in

modulating mucosal immunity and the intestinal microbiota—particularly the levels of lactic acid bacteria (LAB).

Members of *Enterococcus* and *Candida* share certain similarities, including their emergence as opportunistic pathogens after a long nonpathogenic existence in the host microbiome. These microbes can asymptomatically colonize humans, and their pathogenesis generally arises from this asymptomatic colonization (13). Infections involving these organisms are tightly linked to ecological disruption, which may be due to prior antibiotic exposure, treatment with chemotherapeutic agents, medical devices, or anatomic disruption. Consistent with this overlap in clinical presentation, the most severe forms of infection often occur in the same clinical setting—namely, following significant nosocomial exposure, broad-spectrum antibiotic use, and immune defects (14, 15). Furthermore, *C. albicans* and *E. faecalis* are common coconstituents in polymicrobial infections, and outgrowth of one of these organisms promotes the outgrowth of the other (7, 16, 17). Multidrug-resistant *E. faecalis* and *C. albicans* are becoming increasingly common in hospital settings, so by understanding and exploiting the interplay between these organisms and their antagonistic interacting partners (e.g., *Lactobacillus* species), we may be able to enhance the efficacy of existing antimicrobials in treating these opportunistic infections.

Unfortunately, research to date on *Lactobacillus-Enterococcus-Candida* interactions has only examined the cross talk between two of these microbes at a time, and there have been no studies investigating the mechanisms by which *C. albicans* itself interacts with *Enterococcus* or *Lactobacillus* species. In this review, we provide a brief background on each microbe and then examine the existing data on the mechanisms employed by *Lactobacillus* species, *E. faecalis*, and *C. albicans* to modulate each other's growth and/or virulence. We use this information to construct a mechanism-focused model of the microbial ecology of these three microorganisms in the GI tract, highlighting points where their interactions likely affect human health and disease.

CANDIDA ALBICANS

Candida is a diverse genus of fungi consisting of over 200 species, and yet only a few species are known to cause disease in humans (18). One of the most prevalent of these species is *Candida albicans*, which asymptomatically colonizes the human intestinal, upper respiratory, and genitourinary tracts as well as the skin. As a polymorphic fungus, specific environmental cues can trigger *C. albicans* to undergo various morphologic transformations (reviewed in reference 19) that are central to its pathogenesis and elicit different responses from host cells and the surrounding microbiota (20–22). In addition to being one of the most ubiquitous fungal species in the human microbiota, *C. albicans* is most commonly associated with infection, with *Candida glabrata*, *Candida parapsilosis*, *Candida krusei*, and *Candida tropicalis* accounting for most of the remaining infections (23). The clinical spectrum of disease caused by these different species is largely indistinguishable, although *Candida auris* has a greater propensity for localized outbreaks in acute care settings (24). This may be due to direct clonal transmission of *C. auris* via fomites in these settings, whereas other *Candida* species are less resilient on abiotic surfaces and are therefore less likely to seed infections and spread in this way (24, 25).

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Morphologic and phenotypic plasticity. These traits enable *C. albicans* to rapidly adapt to changing environmental conditions and colonize diverse niches. Yeast and hypha are the predominant morphological forms of *C. albicans* encountered in the GI tract during health and disease (19). Yeast cells are round and proliferate by budding, while hyphal cells are filamentous and exhibit polarized growth whereby polarisomes direct germ tube formation and elongation at the apex of the cell (19). The ability for *C. albicans* to transition back and forth from yeast to hypha is generally regarded as its most important virulence factor (19, 26, 27).

As a yeast cell, *C. albicans* may also switch between two distinct phenotypic states named for their colony appearance: "white" and "opaque" (22, 27). Although these

phenotypes are not genetically encoded, they are heritable and exhibit distinct transcriptomic profiles (27). Moreover, white and opaque cells preferentially occupy separate niches and differ in their interactions with immune cells, propensity to mate, and conditions in which they can form hyphae (27, 28). In doing so, phenotypic switching also directly impacts *C. albicans* virulence. Interestingly, passage of *C. albicans* through the GI tract results in a phenotypic switch into the gastrointestinal-induced transition ("GUT") phenotype, which possesses a distinct transcriptome from white or opaque cells (29). In contrast to white cells, which are round or oval, GUT cells are elongated and more closely resemble opaque cells in shape; yet they lack many of their defining characteristics, including heat sensitivity, sexual mating capacity, and increased expression of genes encoding secreted aspartyl proteases (29). While white-opaque switching and GUT are the best-studied phenotypic transitions in *C. albicans*, a number of other phenotypes have been identified (reviewed in references 22 and 30), which may each serve important functions in many aspects of *C. albicans* biology such as generating variability in commensal and pathogenic populations to promote their adaptability.

C. albicans uses quorum sensing (QS) and pheromone signaling to regulate its morphologic and phenotypic states. Notably, hyphal morphogenesis is inhibited under conditions of high cell density by the QS molecule (QSM) farnesol, which is secreted by *C. albicans* in a density-dependent manner (31). Farnesol also acts to repress opaque cell formation and *C. albicans* mating, as it can be produced only by white cells and has even been shown to kill opaque cells (31). In contrast, only opaque cells can secrete pheromones, which promote biofilm formation in white cells as well as sexual mating in opaque cells (31). Host environmental determinants of *C. albicans* morphological and phenotypic states include pH, temperature, and nutrient availability (22). The combinatorial effects of morphology and phenotype on *C. albicans* pathogenesis in different physiological contexts are incompletely understood. Nevertheless, it is clear that the transition from commensal to pathogen is multifaceted and not exclusively a consequence of hyphal morphogenesis.

Cell wall composition. The *C. albicans* cell wall is critical for nearly every aspect of its biology and virulence. In addition to providing protection and maintaining its shape, this structure mediates physical interactions with the host and other microorganisms and enables *C. albicans* to assume various morphologies (32, 33). Not surprisingly, yeast and hyphal cell walls have distinct compositions which are at least partially responsible for their differential recognition by immune cells and the responses they induce (21). Irrespective of its morphological state, the *C. albicans* cell wall is composed primarily of carbohydrates and heavily glycosylated proteins organized into an inner and outer layer (21, 32). The three major carbohydrates include β-glucans, chitin, and mannose polymers, which may be interspersed or directly associated with cell wall proteins (21, 33). β-Glucans and chitin comprise the inner layer adjacent to the plasma membrane and provide shape and rigidity to *C. albicans* cells, while mannose polymers covalently linked to proteins (termed mannoproteins or "mannans") dominate the outer layer and control cell permeability but not overall strength or shape (21, 32). Characterization of yeast- and hypha-specific expression of cell wall structures has proven to be a challenge due to the inherent dynamism of *C. albicans* in physiological settings. However, certain cell wall components are linked to functions critical for *C. albicans* virulence, including adhesion, biofilm formation, and interactions with immune cells (reviewed in references 32 and 33).

Metabolism and respiration. *C. albicans* requires exogenous sources of carbon, nitrogen, and phosphate for biosynthetic processes as well as pathogenesis. The preferred carbon source of *C. albicans* is glucose; however, it demonstrates a high degree of metabolic plasticity which allows it to exploit a variety of both fermentable and nonfermentable carbon sources (34, 35). This versatility also enables *C. albicans* to colonize diverse nutritional niches in the host and outcompete other microorganisms for growth-limiting nutrients (26, 35). For example, when faced with sugar-limiting conditions, *C. albicans* upregulates genes involved in amino acid transport and metabolism,

allowing it to simultaneously assimilate carbon and nitrogen from those amino acids (34). Nitrogen can also be derived from proteins, and several secreted proteases involved in nitrogen acquisition from protein sources are important virulence factors for *C. albicans* (36–38). Phagosomes are nitrogen-deficient environments, so internalization of fungi by macrophages or neutrophils triggers an upregulation of amino acid biosynthetic pathways to boost nitrogen intake (39–41).

Phenotypic analysis of *C. albicans* in the presence of different metabolic cues reveals striking differences in optimal growth requirements between white and opaque cells (42), suggesting that these two phenotypes are metabolically specialized for different host niches. In addition, the altered transcriptome of GUT cells reflects an enhanced fitness and commensalism of this phenotype in the mammalian GI tract, as gene expression is skewed toward the metabolism of nutrients encountered there (29). Specific differences in the metabolic pathways of white, opaque, and GUT cells are discussed more in reference 29.

C. albicans metabolism is greatly affected by oxygen levels. As a facultative anaerobe, it grows optimally under aerobic conditions but is capable of both aerobic respiration and anaerobic fermentation (35). The GI tract is largely hypoxic, although steep oxygen gradients exist between the upper and lower GI tracts as well as from the lumen to epithelium (43). This normally restricts microbes to specific regions based on their oxygen tolerances. However, thanks to its metabolic flexibility under fluctuating oxygen levels, *C. albicans* can thrive in diverse anatomical niches (35). When grown *in vitro* under microaerophilic conditions, *C. albicans* exhibits enhanced hyphal growth and biofilm formation as well as β-glucan masking on its cell wall, suggesting that low oxygen promotes its virulence (44–46). In a recent study comparing the metabolomes of *C. albicans* grown under hypoxic (i.e., 5% oxygen) or aerobic conditions, stark differences were revealed in fundamental metabolic pathways, including glycolysis and cell wall biogenesis (35). These observations suggest that the low oxygen levels encountered in the GI tract promote *C. albicans* pathogenesis, and yet, *C. albicans* colonizes most humans without causing infection. Crucially, none of the aforementioned studies account for the effects of surrounding microbial or host cells, which likely alter or interfere with the responses reported in *C. albicans* monocultures.

Colonization of Mucosal Tissues

Although over 99% of the microbial genes in the human microbiome are bacterial, there has been a growing appreciation for the role of the minor fungal component ("mycobiome") in human health (47, 48). *C. albicans* is one of the most abundant fungal species in the mycobiome and is estimated to be present in around 60% of healthy adults (49); although, these colonization rates are reported to be lower in non-Westernized societies (50). *C. albicans* is also the most common cause of a variety of life-threatening fungal diseases collectively referred to as "candidiasis," which are typically seeded by indigenous *Candida* populations (47, 51). Nearly all mucosal surfaces can be colonized by *C. albicans*, but its primary habitats include the oral cavity, GI tract, and vaginal canal. In a given individual, *C. albicans* isolates from different anatomical regions are often genetically similar but nonidentical, indicating that they adapt to distinct selective pressures in these regions (52). Its presence at each site is implicated in a number of fungal infections—each with potentially unique target populations and clinical manifestations. However, the focus of this review is on the interactions of *C. albicans* in the GI tract because that is the major reservoir for disseminated candidiasis and where *Enterococcus faecalis* and many *Lactobacillus* species also reside.

Gastrointestinal tract. The human GI tract can be broken up into the following three major sections: upper (esophagus and stomach), middle (small intestine, which includes the duodenum, jejunum, and ileum), and lower GI tract (colon and rectum). Sampling different regions of the human GI tract for characterization of their microbial communities is a complicated and invasive undertaking. In a 2018 study (53), stool samples from healthy adults were inoculated into bioreactors simulating the different nutritional conditions and oxygen saturation found in these two regions. Bioreactors

representing the upper-middle GI tract (i.e., high levels of simple sugars and hypoxic conditions) had reduced bacterial diversity but elevated levels of *C. albicans* compared with the lower GI tract bioreactors containing low sugar under anoxic conditions (53). *Candida* abundance in the GI tract is also significantly influenced by short-term diet since a high consumption of carbohydrates within a single week is associated with higher fungal burdens (54). As *C. albicans* coexists with the bacterial microbiota and diet has been shown to strongly modulate bacterial enterotypes (55), diet-associated changes in *C. albicans* abundance are likely affected by changes in the levels of certain bacteria and/or their metabolites.

Gnotobiotic mice have been used to evaluate the localization of *C. albicans* across the mammalian GI tract and understand its spatial organization in the presence or absence of enteric bacteria (56, 57). Strikingly, fungal distribution is dependent on the presence of bacteria. As the sole colonizer, *C. albicans* was found both in the intestinal lumen and adjacent to the mucus layer along the entire murine GI tract, but the addition of the enteric bacterium *Bacteroides thetaiotaomicron* led to the formation of a thick outer mucus layer in which *C. albicans* became embedded (56). *B. thetaiotaomicron* is known to promote mucin secretion by goblet cells in the GI tract and directly interact with *C. albicans* cell wall mannans to inhibit fungal growth (56, 58), so its presence likely impacts *C. albicans* colonization. Indeed, *B. thetaiotaomicron* and *C. albicans* were in close association with one another, and *B. thetaiotaomicron*-processed mucins supported the growth of *C. albicans* to a greater extent than unprocessed mucins (56). Taken together, these data suggest that *C. albicans* primarily inhabits upper-middle regions of the GI tract, adjacent to or within the mucus layer. Other studies using gnotobiotic mice (57, 59–61) and piglets (62, 63) have detected high levels of *C. albicans* in the lower GI tract as well, supporting the notion that *C. albicans* colonizes throughout the GI tract.

Oral cavity and urogenital tract. Fungal-bacterial interactions also play an important role in balancing *C. albicans* commensalism and pathogenesis in the oral and urogenital tracts, so understanding their interactions in these niches may provide insight into their cross talk in the GI tract. *C. albicans* colonization and infection in the oral and vaginal mucosae are not the focus of this review, but more detail is provided in references 64 and 65.

Establishment of the oral microbiome begins at birth and later expands downstream in the GI tract (66). Crucially, the factors that shape the oral microbiota such as diet and oral hygiene can also impact the microbial composition of the GI tract. *Candida* species are the most frequently encountered fungi in the oral cavity, appearing in an estimated 75% of healthy individuals (67). *C. albicans* can grow as a biofilm in both aerobic environments like the mouth and anaerobic environments such as the colon, but its subsequent virulence greatly depends on its interactions with neighboring bacteria; hence, biofilm formation does not necessarily lead to infection. As a matter of fact, *C. albicans* biofilms in the oral cavity may provide an anoxic niche for many anaerobic bacteria that inhibit its pathogenesis (44).

In addition to the oral cavity, *C. albicans* is the most frequently identified fungal species in the human urogenital tract—particularly the vagina, where it is present in anywhere from 5% to 20% of healthy individuals (64, 68, 69). Given the pronounced differences between these two mucosae in terms of host defense mechanisms, surrounding microbial communities, and overall architecture (69), this further exemplifies the tremendous adaptability of *C. albicans*. The mechanisms underlying *C. albicans* commensalism in the vaginal mucosa may be especially useful in forming hypotheses about its interplay with bacteria in the GI tract. In particular, the healthy human vagina is dominated by *Lactobacillus* species (70), of which many are also present in the GI tract and have been shown to directly antagonize *C. albicans*. Reference 71 provides a comprehensive summary of the role of lactobacilli in preventing the pathogenesis of *C. albicans* and other microbes in the vagina.

Intriguingly, *C. albicans* pathogenesis does not occur at the same rates or under the same circumstances between the oral cavity and urogenital tract. Oropharyngeal

candidiasis (OPC) occurs much less frequently in humans than vulvovaginal candidiasis (VVC), which is likely due to microbiological differences in *C. albicans* itself as well as differences in surrounding microbial communities and host defense. Indeed, despite higher colonization rates in the oral cavity, OPC occurs almost exclusively in immunocompromised individuals, whereas 75% of all women experience at least one episode of VVC in their lifetime, regardless of immune status (69). While infections of the oral and vaginal mucosae are not the topic of this review, it is important to remember the variable nature of *C. albicans* in different niches when making generalizations about its pathogenesis.

Pathogenesis

Prevalence and risk factors. *C. albicans* ranks among the top four most common causes of health care-associated bloodstream infections (BSIs) in the United States, with an estimated mortality rate of 40% to 55% (72). In addition to BSIs (termed "candidemia"), infections can be localized—as in OPC and VVC—or invasive, with invasive candidiasis (IC) accounting for the majority of deaths (73, 74). Notably, over 60% of IC cases across the globe are attributable to *C. albicans* derived from indigenous populations in the GI tract (73, 75). Thus, *C. albicans* represents a significant threat to human health.

There are many well-established risk factors for *C. albicans* infections. Candidiasis is especially prevalent in intensive care units (ICUs), where high doses of antibiotics and immunosuppressive drugs are regularly administered to patients (72). Using a conditional logistic regression model, Wenzel and Gennings (76) projected that ICU patients exposed to antibiotics have a 10% to 30% chance of succumbing to a *C. albicans* BSI, and by adding just one other risk factor (e.g., prior colonization with *C. albicans*), that likelihood jumps to 50%. According to this study, simply being admitted to an ICU carries an inherent risk of over 33%. Antibiotics can sufficiently reduce the levels of antagonistic bacteria to enable *C. albicans* outgrowth and have been successfully used to colonize mice with stable levels of *C. albicans* (11, 12, 77) since mice typically lack indigenous populations of this fungus (78). Similarly, immunodeficiencies due to chemotherapy or other immunosuppressive drugs (79), underlying neutropenia (80), and/or infection with human immunodeficiency virus (HIV) (65) are considerable risk factors in the development of candidiasis, although the latter is primarily associated with OPC. These and other predictors for *C. albicans* infections are extensively reviewed in reference 73.

Host innate immunity. Phagocytes are responsible for the elimination of *C. albicans* and critical for preventing systemic candidiasis. Toll-like receptors (TLRs) and C-type lectins on the surface of neutrophils and macrophages recognize β-glucans and mannans on the fungal cell wall, leading to either pro- or anti-inflammatory responses (81, 82). Stimulation of TLR2 by *C. albicans* can trigger the production proinflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin-1α (IL-1α), IL-1β, and IL-6, while stimulation of TLR4 results in chemokine production and thus enhanced neutrophil recruitment (82, 83). Moreover, the innate immune receptors TLR2, TLR4, Dectin-1, and mannose recognize different structures in the *C. albicans* cell wall and can elicit different responses as a result (82). Phagocytosis of *C. albicans* by neutrophils is mediated by β-glucans (84), although β-glucans can also trigger residual cytokine production in other cells (82). The β-glucan layer is typically "masked" by the outer mannan layer, enabling *C. albicans* to evade recognition by host cells (85). Cell wall remodeling that results in the masking and unmasking of β-glucans is therefore an important mechanism by which *C. albicans* modulates its survival and virulence in a host. β-Glucan expression is considerably reduced on hyphal cells, which is associated with enhanced virulence and reduced induction of proinflammatory cytokine or chemokine release compared with yeast cells (81). Cell wall chitin is recognized by NOD2, TLR9, and mannose receptor, leading to the release of the anti-inflammatory cytokine IL-10 (86). This response likely represents the restoration of the immune balance once a *C. albicans* infection has been controlled. Strains of *C. albicans* isolated from active disease often have considerably higher chitin content than commensal isolates, and any damage to β-glucans may expose more chitin to host receptors, thereby dampening the host immune response (86,

87). As such, immune responses to *C. albicans* are greatly influenced by its morphology. Taken together, innate immunity to *C. albicans* is largely context dependent and determined by both the host cell type/receptor and fungal morphology.

Virulence factors. Some of the most widely recognized factors contributing to *C. albicans* virulence include adhesion, hyphal morphogenesis, biofilm formation, and phenotypic switching (88). Specialized cell wall proteins called adhesins mediate adherence to host cells and other microorganisms, as well as abiotic surfaces, such as intravenous (i.v.) catheters. The agglutinin-like sequence (ALS) and hypha-associated GPI-linked proteins are among the best studied of these adhesins and are both significantly upregulated during infection (89–91). Following initial adherence to biotic or abiotic surfaces, *C. albicans* may proliferate and form biofilms enclosed by a protective extracellular matrix that enhances its resistance to host and microbial defense mechanisms (88). Hyphal morphogenesis is also essential for *C. albicans* pathogenesis, as is evidenced by the fact that mutants unable to form hyphae are avirulent (92, 93). However, the propensity for *C. albicans* to undergo hyphal morphogenesis is in large part determined by its phenotypic state and vice versa (22). While both white and opaque cells undergo filamentation *in vivo*, white cells more readily establish lethal systemic infections in a host, which is predominantly temperature dependent (28). Furthermore, white cells are more susceptible to phagocytosis by macrophages than opaque cells, indicating that these phenotypes interact differently with immune cells (28). Interestingly, the observed hypervirulence of white cells is also dependent on their ability to undergo filamentation, as deletion of genes regulating hyphal morphogenesis significantly reduces the lethality of infection (28).

A recent review by Kumamoto and colleagues (94) highlights several studies in which expression of hypha-specific genes was associated with attenuated colonization fitness in the mouse GI tract. Of note, serial passage of *C. albicans* in antibiotic-treated mice promoted *C. albicans* competitive fitness by selecting for mutations in *FLO8* and *EFG1*, which are required for hyphal morphogenesis (95). Similarly, *C. albicans* mutants with deletions in the hyphal-associated genes *EFG1*, *BRG1*, *TEC1*, *ROB1*, and *UME6* were able to outcompete the wild-type strain in the mouse GI tract, whereas a *UME6*-overexpressing mutant had significantly reduced fitness (96). Surprisingly, the *UME6*-knockout strain displayed a hyperfit phenotype but retained a normal ratio of yeast and hyphae, indicating that morphology alone does not dictate commensal fitness. Although these data suggest that hyphae have a competitive disadvantage, *C. albicans* typically colonizes the GI tract as a mixture of yeast and hyphal cells (94, 96), so the ability to transition between yeast and hyphal forms is likely important for commensal colonization.

The proximal GI tract has been reported to be dominated by yeast while hyphae predominate the lower GI tract (96), suggesting that tissue-specific signals are involved in the control of hyphal transformation. This may also reflect differences in antihyphal signals from bacteria (especially LAB) in those regions. Together, these observations raise the intriguing possibility that inhibition of hyphal morphogenesis by *Lactobacillus* species actually enhances its fitness rather than reducing its virulence. However, it is important to keep in mind that lactobacilli affect many aspects of *C. albicans* biology which can outweigh the effect of hyphal suppression on colonization, so the net impact of their interactions may be a decreased growth of *C. albicans* in the GI tract.

Among the lesser-known virulence factors are secreted molecules involved in host cell penetration and pH sensing and regulation and various proteins involved in environmental stress responses, which are discussed at length in reference 88. Importantly, *C. albicans* virulence factors can be antagonized by various components of the host immune system and surrounding microbiota and represent potential targets for antifungal drugs. However, because *C. albicans* virulence factors are so interconnected, it is critical to include readouts such as host survival or inflammation in any *in vivo* infection model when making claims about the impact of a specific condition or organism on *C. albicans* pathogenesis.

Prostaglandins and mucosal immunity. The production of bioactive lipid mediators is only one of many mechanisms by which *C. albicans* directly interacts with and alters the surrounding immune milieu to promote its survival. Prostaglandins can be synthesized by host cell cyclooxygenases that act on arachidonic acid released from the plasma membrane by phospholipases (97). Host-derived prostaglandin E_2 (PGE_2) is one of the signals for hyphal transformation in *C. albicans* (92, 98–100). Interestingly, *C. albicans* is capable of producing authentic PGE_2 as well as functionally related cross-reactive oxylipins from host-derived arachidonic acid (97–101) via an unconventional pathway involving a fatty acid desaturase (Ole2) and multicopper oxidase (Fet3) (101). Both host and fungal PGE_2 shift the adaptive immune response in favor of fungal survival by promoting Th2 responses and thus inhibiting anti-*Candida* Th1 responses, lymphocyte proliferation, and phagocytosis (97).

In addition to prostaglandin production, *C. albicans* colonization of the GI tract can modulate mucosal immunity and barrier function. In antibiotic-treated mice, GI colonization by *C. albicans* can promote the development of a $CD4^+$ Th2 cell-mediated allergic airway response to mold spore challenge (5, 6). Subsequent studies have shown that M2 macrophage polarization in the lung is a critical component of the response, and suppression of PGE_2 synthesis blocks this polarization, resulting in decreased allergic airway inflammation (102). *C. albicans* colonization of mice also significantly enhances GI epithelial leak of orally delivered OVA and drives an increase in the number of mast cells in the intestinal mucosa (103, 104). IL-9 production and mast cell activation are critical steps in the process whereby *C. albicans* induces epithelial barrier leak (104). Additional evidence of a positive feedback loop between *C. albicans* colonization and intestinal inflammation has also been reported in a mouse model of dextran sulfate sodium (DSS)-induced colitis in which *C. albicans* colonization was enhanced by inflammation-inducing injury to the intestinal epithelium (105).

Clinical Significance

The clinical spectrum of candidiasis is associated with the immune status of the patient. In immunologically intact patients, the most common manifestation is VVC, which is generally well treated with localized therapy (106). However, even in immunocompetent hosts, recurrent VVC impacts an estimated 138 million women each year (107). OPC and other superficial mycoses can last longer in patients with defects in cellular immunity, such as those with AIDS or those receiving high doses of corticosteroids (108, 109). *C. albicans* can also cause severe invasive infection, which is tightly linked to neutropenia and ICU exposure (110, 111). In these patients, IC can be indistinguishable from bacterial sepsis (112). Invasive focal infections, such as endocarditis and endophthalmitis, are due to seeding by indigenous *C. albicans* following systemic infection or introduction from devices such as intravenous (i.v.) catheters and ventricular shunts or i.v. drug use (113, 114). Additionally, chemotherapeutic agents which lead to disruption of mucous membranes increase the risk for systemic infections, presumably because they also facilitate entry of organisms from the GI tract into the bloodstream. Interestingly, *Candida* pneumonia is extraordinarily rare (115), as is pneumonia due to *Enterococcus* species (116). *Candida* pneumonia has historically been attributed to contamination of the airways by oral *C. albicans*, but positive sputum cultures and bronchoalveolar lavage cultures are not uncommon (117, 118). More recently, recognition of the continuity of the microbiome between the upper and lower airways has raised the significant possibility that *Candida* isolation in those sites may not represent contamination (118).

LACTIC ACID BACTERIA

Broadly speaking, the term lactic acid bacteria (LAB) refers to a group of bacteria that produce lactic acid as the primary by-product of carbohydrate metabolism. More precisely, LAB belong to the order *Lactobacillales* and actually constitute an extremely diverse group in terms of metabolic pathways, tolerances to environmental stresses, pathogenic potential, and ecological niches (119). While LAB are often equated with

Lactobacillus species or other generally harmless or even beneficial bacterial strains, this group also includes common human pathogens—most notably *E. faecalis*.

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LAB are Gram-positive, non-spore-forming, aerotolerant anaerobes that ferment a variety of carbohydrates to lactic acid and are generally oxidase, catalase, and cytochrome negative (120). Most LAB are fastidious organisms and require complex nutrients for growth, including amino acids, vitamins, and minerals (121). Although lacking heme enzymes involved in oxidative stress response (119), LAB can use alternative radical scavenging metals such as manganese (122), zinc (123), and selenium (124). The absence of cytochromes in LAB means that they cannot use oxygen to generate ATP by means of an electron transport chain. Instead, they rely on sugar fermentation, which generates lactic acid either exclusively (i.e., homolactic fermentation) or in conjunction with other end products (i.e., heterolactic fermentation) (125). However, in addition to fermentation, LAB can generate ATP from noncarbohydrate substrates through pathways that also serve to counteract the acidification caused by lactic acid accumulation (119).

The LAB group encompasses many well-known genera including *Lactobacillus*, *Enterococcus*, *Lactococcus*, and *Streptococcus* (119, 126). Subgroups of LAB that were originally proposed by Orla-Jensen in the early 20th century are still used to this day (126). The classification criteria include morphology (rods versus cocci), fermentation pathway (homofermentative versus heterofermentative), optimal growth temperatures, carbon dioxide production (from glucose versus gluconate), requirement for thiamine, ability to reduce fructose to mannitol, and ability to hydrolyze arginine. Reference 126 provides a more complete overview of these subgroups.

Colonization and Distribution

The heterogeneity of LAB as a group is evidenced by their presence in diverse niches, including the human GI and vaginal tracts, dairy and meat products, soil and decomposing plant material, and sewage water (127). LAB comprise a staggering 90% to 100% of the vaginal microbiota (which is predominantly *Lactobacillus* species [128]) and inhabit every major region of the GI tract (Fig. 1).

In humans, microbial levels in the upper regions of the GI tract are restricted by extremely low pH, toxic bile salts, oxygen tension, and fast-flowing digesta (129). Consequently, bacterial load is relatively low (10^1 to 10^3 microbes per gram in the stomach and duodenum [130]), as is the overall microbial diversity (131, 132), making the proportion of LAB in these regions comparatively high (Fig. 1). The colon is home to the highest microbial diversity and abundance, with numbers reaching an estimated 10^{11} per gram of contents (130). Although absolute numbers of LAB are relatively stable from the upper to lower GI tract (131), they represent a much smaller fraction of the total bacteria in the distal regions of the small intestine to the rectum (Fig. 1).

Given the high proportion of LAB in areas with extremely low bacterial abundance and diversity, their interactions with other microorganisms in these niches are likely to have a significant influence on human health. Indeed, the genera *Lactobacillus* and *Enterococcus* have received considerable attention for their roles in colonization resistance, microbial carriage, opportunistic infection, and host immunity.

Lactobacillus Species

Microbiology. *Lactobacillus* species can be either aerotolerant or anaerobic, exist as rods or coccobacilli, and have moderate to high tolerance to salt and acid. Their unusually high resistance to low pH is thought to be mediated by the F_0F_1-ATPase, which establishes a proton gradient across their membrane (133, 134). Furthermore, many lactobacilli carry bile salt hydrolase (BSH) proteins that enable them to tolerate high concentrations of bile acids in the small intestine (135, 136). As LAB, they have complex nutritional requirements and produce lactic acid as a by-product of sugar fermentation. More precisely, lactobacilli can be either homofermentative (i.e., generate at least

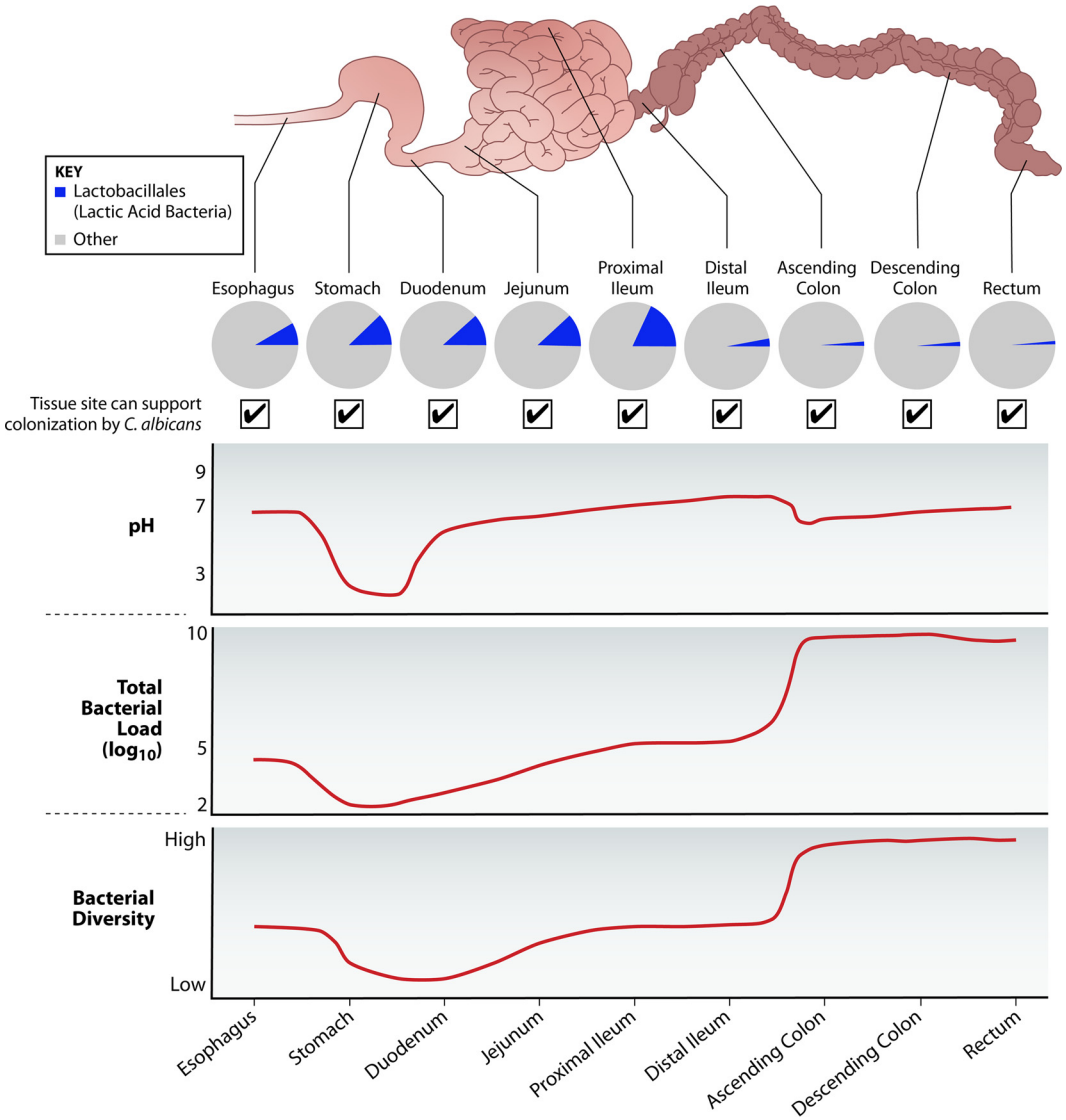

FIG 1 Distribution of LAB and *C. albicans* along the human GI tract. LAB including *Lactobacillus* and *Enterococcus* species belong to the order *Lactobacillales*, which are found in proportionally higher numbers in the upper GI tract. The predominance of LAB in proximal regions such as the stomach and small intestine is a result of their tolerance to the extremely low pH, bile salts, and oxygen gradients within those niches. Although the total number of LAB is relatively stable throughout the GI tract, the total bacterial load and diversity increase dramatically starting at the ileocecal junction, so their relative abundance is much lower in the large intestine (131, 132). The fact that LAB abound in microbially sparse regions suggests that whatever interactions they have with other cells in those regions play a significant role in their functioning as well as host physiology. Importantly, *C. albicans* is also found in every region of the GI tract, including these low-biodiversity niches, so the interplay between LAB and *C. albicans* is expected to have a profound impact on host health.

85% lactic acid from fermentation) or heterofermentative (i.e., generate equal amounts of lactic acid, ethanol and/or acetic acid, and CO_2 from fermentation) (137).

Colonization of the gastrointestinal tract. The exact numbers and species of *Lactobacillus* present in the human GI tract at any given moment have been highly variable across studies and cohorts (128). This lack of consistency makes it difficult to distinguish stably colonizing species from transient species, which are predominantly derived from the consumption of *Lactobacillus*-containing foods such as yogurt, cheese, and pickles. Nevertheless, there are some species that are more commonly detected in human samples and not generally present in food (e.g., *L. acidophilus*, *Lactobacillus crispatus*, *Lactobacillus salivarius*, *Lactobacillus gasseri*, *L. johnsonii*, and

Lactobacillus reuteri) (138), suggesting that they may be indigenous to the human GI tract. In addition, 16S rRNA and terminal restriction fragment length polymorphism (T-RFLP) analyses repeatedly demonstrate that *Lactobacillus* species constitute an appreciable fraction of the microbial population in those regions. This includes the identification of lactobacilli in gastric (139–141) as well as jejunal and ileal (142, 143) biopsy specimens from healthy humans. Considerably higher numbers of lactobacilli are found to persist in the GI tracts of other animals (138), which has been proposed to be due to differences in the epithelium that potentiate *Lactobacillus* adhesion (144).

Impact on human health. Of the LAB, lactobacilli are most closely associated with health benefits. Moreover, despite the plethora of strains present in both humans and the environment, very few have been proven to have any pathogenic potential (145). A report drafted by the joint FAO/WHO Working Group (146) notes that *Lactobacillus* is one of two bacterial genera most commonly exhibiting probiotic attributes—i.e., conferring health benefits on the host. The ability of lactobacilli to not only withstand the hostile environments of the stomach and proximal small intestine but also persist in the lower GI tract make them viable for orally administered probiotics. More importantly, many *Lactobacillus* species have been shown to have antagonistic effects on a variety of pathogens both *in vitro* and *in vivo* (for a comprehensive review, see reference 130).

Reduced levels of *Lactobacillus* in the GI tract are correlated with a number of human diseases, including irritable bowel syndrome (IBS), type 1 diabetes, HIV, multiple sclerosis, colon cancer, and allergies (128, 147). It is difficult to ascertain the relative contribution of (i) disease onset that leads to an inhospitable environment for lactobacilli or (ii) *Lactobacillus* depletion by some other means that promotes disease onset. In either case, administration of probiotic *Lactobacillus* species can sometimes significantly improve symptoms (148–151). This suggests that the intrinsic metabolic activities or properties of *Lactobacillus* can benefit their host by modulating the microbiota and/or mucosal immune responses. For example, oral administration of *L. johnsonii* can protect mice in a murine model of cockroach antigen-induced allergic airway disease (4). Lactobacilli produce butyrate and other short-chain fatty acids (SCFAs) following pyruvate fermentation (152, 153), which play important roles in promoting colonic mucosal function and regulating inflammatory responses (154, 155). Importantly, butyrate isolated from *Lactobacillus* cultures can inhibit *C. albicans* hyphal morphogenesis (92). Given that lactobacilli and *C. albicans* are present in all regions of the human GI tract, including the low-biodiversity niches of the stomach and small intestine, *Lactobacillus* species may be central to preventing the outgrowth of *C. albicans* and other similarly resilient opportunistic pathogens.

Enterococcus Species

Microbiology. *Enterococcus* species are broadly characterized as non-spore-forming, ovoid, facultative anaerobes (156). In contrast to lactobacilli, they are exclusively homofermentative and can be either harmless or pathogenic (156). Enterococci can survive under an exceptionally wide range of environmental stresses, including temperature (5 to 50°C), pH (4.5 to 10), oxygen (aerobic or anaerobic), and bile salts (up to 40% [wt/vol]) (157). Importantly, pathogenic strains possess highly plastic genomes and are able to transfer genetic material from their environment via pheromone-responsive conjugative plasmids and can therefore acquire exogenous antimicrobial resistance genes and/or other genes that might increase their virulence or propensity to cause infection (156, 157). Together, these attributes account for the broad distribution of *Enterococcus* species in fermented food and dairy products, aquatic and soil environments, plants, and GI tracts of mammals as well as insects and reptiles (158).

Colonization of the gastrointestinal tract. Enterococci are core members of the human microbiome and are estimated to be 10 to 100 times more abundant than lactobacilli in the GI tract (158). *Enterococcus* species have been isolated from every major region of the GI tract, including the largely inhospitable stomach environs, but are predominantly found in the jejunum, ileum, cecum, and rectosigmoid junction (142). The

remarkable hardiness of enterococci, combined with their genomic plasticity and ability to produce antimicrobial compounds, can impart a considerable competitive advantage to these bacteria within the microbiota. Moreover, pathogenic species such as *E. faecalis* can exploit their intrinsic and acquired antibiotic resistance to proliferate and dominate the GI tract in the event of an antibiotic-induced disruption of the surrounding microbiota (11, 12, 159). Given that some *Enterococcus* species are opportunistic pathogens that can cause serious infections (156), there is a critical need to better understand their interactions with microbes that share their niches and antagonize their growth and/or pathogenesis.

Clinical significance. Similar to *C. albicans*, *Enterococcus* species can cause a broad range of clinical infections when the opportunity presents itself. Notably, although the genus *Enterococcus* is comprised of 34 species, the vast majority of infections are caused by just two species, namely, *E. faecalis* and *Enterococcus faecium* (156, 160). Their clinical presentations are similar, but their epidemiology and antimicrobial resistance patterns differ, leading to distinct clinical challenges (161). Both are common causative agents of a variety of nosocomial infections, with *E. faecalis* being more common in clinical infections following antibiotic regimens but having more favorable clinical outcomes relative to *E. faecium* (162–164). These species have attributes that facilitate their persistence in the health care environment, including tolerance to desiccation and acidic environments, and have a particular proclivity to acquire antibiotic resistance. *E. faecalis* is generally susceptible to ampicillin, whereas *E. faecium* is more frequently resistant. Both species can harbor vancomycin resistance through the acquisition of a transposon-encoded vancomycin resistance cassette (156, 160, 165).

Localized infection can result from inoculation of organisms from the gastrointestinal tract into the urinary tract, wounds, or peritoneum and may subsequently lead to systemic infection (156, 160–170). Both *E. faecalis* and *E. faecium* can cause endocarditis, and although *E. faecalis* is more frequently the instigator, *E. faecium* also presents a significant therapeutic challenge—particularly ampicillin- and vancomycin-resistant isolates (168). The microbiological attributes that promote enterococcal persistence along with their intrinsic and acquired resistance to many first-line antibiotics have led *E. faecalis* and *E. faecium* to become significant problems in critical care settings, especially for patients with hematological malignancy, extensive antibiotic exposure, and/or prolonged hospitalization (169).

INTERACTIONS BETWEEN LACTOBACILLI AND *C. ALBICANS*

Exopolysaccharides

Bacterial surface polysaccharides, including lipopolysaccharides (LPSs), capsular polysaccharides (CPSs), and exopolysaccharides (EPSs), are key mediators of adherence, biofilm formation, and evasion of host defenses (171). In addition to their role in pathogenesis, surface polysaccharides are thought to be involved in the probiotic activity of certain *Lactobacillus* strains. *Lactobacillus rhamnosus* GG harbors galactose-rich EPS molecules on its surface which contribute to its stable colonization in the GI tract and consequently improve its capacity to antagonize pathogens (171).

Tissue adhesion and hyphal morphogenesis are two requisite events in *C. albicans* pathogenesis, so many of the identified probiotic interference mechanisms involve inhibition of one or both of these processes. Specifically, the galactose-rich EPSs of *L. rhamnosus* GG were found to block adhesion of *C. albicans* to several epithelial cell lines despite low adhesion of *L. rhamnosus* GG itself to these cells (172). Given that *C. albicans* has lectin-like adhesins that can bind bacterial surface polysaccharides such as EPSs, the antiadhesive effects of *L. rhamnosus* GG are likely due to coaggregation with *C. albicans* rather than competitive exclusion. Furthermore, *L. rhamnosus* GG EPSs reduced the ratio of hyphae to yeast cells in a dose-dependent manner (172). Interestingly, this study found that EPS-deficient *L. rhamnosus* GG mutants that harbored other galactose-rich molecules were also able to inhibit hyphal morphogenesis, indicating its antihyphal activity is due to the presence of galactose-rich polymers and

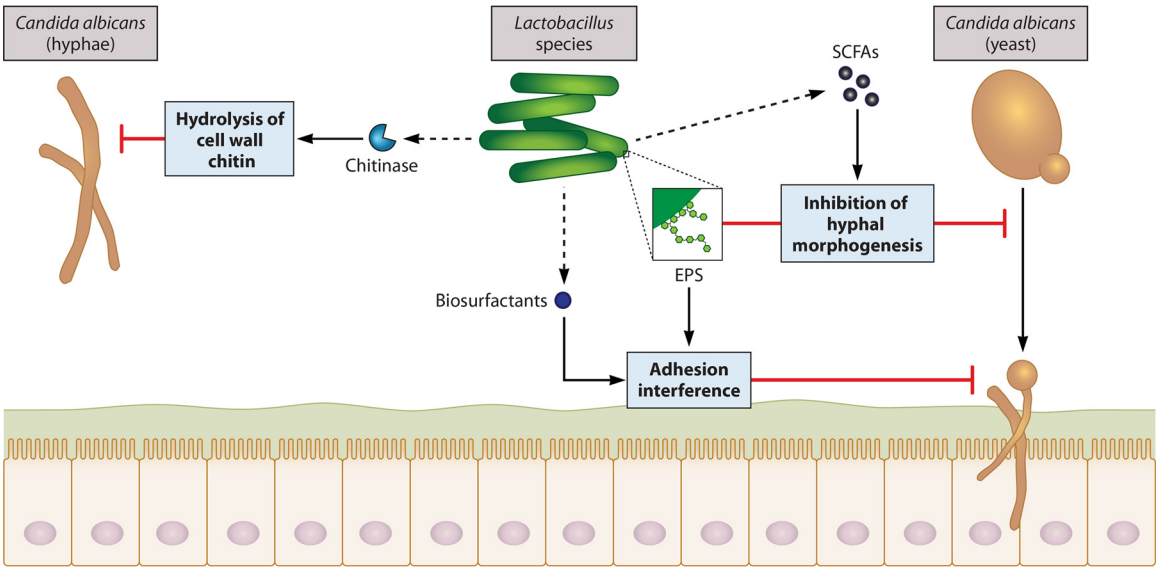

FIG 2 Mechanisms of interaction between *Lactobacillus* species and *C. albicans*. Lactobacilli antagonize both the growth and pathogenesis of *C. albicans* in the GI tract via secreted and cell surface molecules. Some *Lactobacillus* species secrete hydrolytic enzymes that can degrade components of the *C. albicans* cell wall that are critical for immune evasion and pathogenesis. Notably, *L. rhamnosus* GG and *L. johnsonii* can produce proteins with chitinase activity that hydrolyze cell wall chitin and thus reduce *C. albicans* growth and hyphal morphogenesis. Exopolysaccharides (EPSs) present on the cell surface of lactobacilli mediate adherence to mucosal surfaces and sustained colonization of the GI tract, which enhances their capacity to antagonize pathogens. While some forms of EPSs may prevent *C. albicans* biofilm formation by blocking potential mucosal binding sites, the antiadhesive effect of *L. rhamnosus* GG is due to coaggregation with *C. albicans*, as its EPS has a low affinity for epithelial cells but can bind lectin-like adhesins on *C. albicans*. Galactose-rich EPSs on *L. rhamnosus* GG are also thought to inhibit *C. albicans* hyphal morphogenesis, although the exact mechanism still needs to be resolved. Lactobacilli produce short-chain fatty acids (SCFAs) from the fermentation of carbohydrates, which interfere with hyphal morphogenesis and biofilm formation. Finally, some *Lactobacillus* species secrete amphipathic biosurfactants which block *C. albicans* adherence to the intestinal epithelium by altering the electrochemical properties of the host-microbial interface.

may not be dependent on EPSs per se. A mutant lacking SpaCBA pili was still able to reduce the number of hyphal cells, demonstrating that pili are not critical for colonization resistance against *C. albicans* like they are for enterococci (172, 173). Galactose-rich surface EPSs thus constitute one of the mechanisms by which *Lactobacillus* species can antagonize *C. albicans* in the GI tract (Fig. 2).

Short-Chain Fatty Acids

An essential role of lactobacilli in the gut microbiota is to metabolize partially and nondigestible carbohydrates into short-chain fatty acids (SCFAs). The three major SCFAs are butyrate, acetate, and propionate, which have a number of health-promoting effects, including maintaining the structure, integrity, and function of the intestinal epithelium; inhibiting proinflammatory immune responses; and stimulating the production of mucin (reviewed in reference 174). Crucially, many of these volatile fatty acids also exhibit antimicrobial activities against *C. albicans* and other pathogens (92, 175–177).

While attempting to identify specific factors in serum involved in *C. albicans* hyphal morphogenesis, it was observed that coculture of *C. albicans* with live—but not heat killed—lactobacilli significantly reduced germ tube formation, which suggested that metabolic activity is necessary for their inhibitory activity (92). Interestingly, spent culture supernatants from each of the *Lactobacillus* strains used in that study (*L. casei*, *L. paracasei*, and *L. rhamnosus* GG) also ablated *C. albicans* germ tube formation, indicating that this inhibitory effect is mediated by a secreted metabolic by-product. Of the three commercially available SCFAs tested, only butyrate was found to have a similar effect when added to *C. albicans* cultures at physiologically relevant concentrations (92). Butyrate is therefore the most potent of these SCFAs in blocking hyphal morphogenesis and may be at least partially responsible for the antihyphal activity of many

Lactobacillus species in the GI tract (Fig. 2). But how exactly do these compounds interfere with hyphal morphogenesis? Given that butyrate and other SCFAs have wide-ranging effects on both epithelial and immune cells and that hyphal morphogenesis is a complex process involving many pathways, the answer to this question is likely to involve more than one mechanism.

Butyrate can act as a histone deacetylase inhibitor (HDACi) (178, 179), which is noteworthy because HDACs are thought to control the transcription of genes involved in *C. albicans* yeast-hyphal transitions (180). In one study, synthetic HDACis were shown to significantly reduce *C. albicans* germ tube formation as well as adhesion to human epithelial cells (181). Another group found that butyrate inhibited *C. albicans* growth and filamentation but also enhanced the production of nitric oxide by macrophages and thus their ability to kill *C. albicans* cells (176). While this group did not implement any experiments to directly link the effects of butyrate on *C. albicans* virulence to its function as a HDACi, they hypothesized that that was the likely mechanism (176). The observation that butyrate enhances the antifungal activity of macrophages is indication that SCFAs may also act indirectly by modulating the host immune response to *C. albicans*.

In addition to macrophages and other innate immune cells, SCFAs can influence $CD4^+$ T cells during fungal infection. Stimulation of $CD4^+$ T cells by dendritic cells (DCs) with a *C. albicans* antigen can either promote or dampen inflammatory responses, depending on the $CD4^+$ T cell subset (182). For example, activation of $Foxp3^+$ regulatory T cells (T_{regs}) triggers an anti-inflammatory response that reduces *C. albicans* pathology, while Th17 cell activation leads to the release of chemokines and proinflammatory cytokines (e.g., IL-17A), which augments tissue damage (182). Interestingly, although T_{regs} suppress Th17 responses in the GI tract, they enhance protective Th17 responses during OPC infections (183). In a mouse model of OPC, antibiotic-induced depletion of the bacterial microbiota resulted in reduced numbers of T_{regs} and Th17 cells, corresponding to increased fungal loads and oral pathology (177). Treatment with SCFAs reversed the pathology caused by *C. albicans* and concomitantly increased the numbers of T_{regs} and IL-17A-producing cells (177). Assuming that similar interactions occur in the GI tract, *Lactobacillus*-derived SCFAs may promote protective $CD4^+$ T cell responses to *C. albicans*. In support of this hypothesis, Guinan and colleagues (184) showed that microbial-derived SCFAs protect against *C. albicans* colonization of the mouse GI tract and can inhibit processes associated with its virulence. More specifically, mice treated with cefoperazone had higher fungal loads in their cecal contents, which correlated with significantly lower levels of SCFAs. They also found that physiological concentrations of SCFAs significantly reduced *C. albicans* growth, biofilm formation, and hyphal morphogenesis *in vitro*. Together, these results underscore the importance of SCFA-producing lactobacilli in preventing *C. albicans* infections.

Biosurfactants

A variety of microorganisms, including lactobacilli, secrete amphipathic molecules called biosurfactants, which accumulate at interfaces and are especially important in mediating cell adherence and desorption from surfaces (185). *Lactobacillus* and *Streptococcus* species have been shown to use biosurfactants to displace uropathogenic *E. faecalis* from glass in parallel-plate flow chambers (186). In addition to their effects on pathogenic bacteria, *Lactobacillus*-derived biosurfactants can inhibit fungal adhesion and biofilm formation by altering the hydrophobicity and electrical properties of interfaces.

Interestingly, planktonic growth of a nosocomial *C. albicans* strain was stimulated by high concentrations of a *L. brevis*-derived biosurfactant, while adherent growth and biofilm formation on medical-grade surfaces have consistently been reduced by biosurfactants from a variety of lactobacilli (187, 188). This suggests that biosurfactants do not affect cell viability but rather derive their antifungal activity from their antiadhesive properties. Recently, a biosurfactant from a vaginal *L. crispatus* isolate was shown to inhibit *C. albicans* adhesion to a human epithelial cell line, demonstrating its potential functionality within the GI tract (189). Together, these data illustrate that the secretion

of biosurfactants is a mechanism by which *Lactobacillus* species can suppress *C. albicans* adhesion to the epithelium and thus its pathogenesis in the GI tract (Fig. 2).

Hydrolytic Enzymes

The fungal cell wall is a unique and essential structure that not only provides protection and cell rigidity but also mediates interactions with the external environment. Antifungal drugs typically target cell wall structures such as β-glucans, mannans, and chitin because these components are not present in human cells and are capable of modulating the host immune response to promote fungal dissemination (190). Importantly, *C. albicans* harbors a highly transmutable cell wall that enables it to switch morphologies and transition from a commensal to a pathogen. Compared with the yeast form, hyphae are associated with elevated cell wall chitin (191), which is important for immune evasion and as well as resistance to echinocandin antifungals such as caspofungin (87). Echinocandins target the catalytic subunit of the β(1,3)-glucan synthase Fks1, leading to exposure of the underlying layer of chitin, and so resistance is most often acquired through point mutations in *FKS1*, as illustrated in a study by Lee and colleagues (87). In this study, *C. albicans* that was induced to produce excess chitin showed reduced susceptibility to caspofungin *in vitro* and *in vivo*, and some of these clones had acquired point mutations in *FKS1* even without exposure to caspofungin. Thus, cell wall chitin constitutes an important *C. albicans* virulence factor and may be targeted by bacteria with antifungal activity.

In an effort to elucidate the mechanisms by which certain lactobacilli block *C. albicans* hyphal morphogenesis, an assortment of *Lactobacillus* strains was evaluated for their relative ability to block *C. albicans* hyphal morphogenesis and biofilm formation. These experiments identified the closely related species *L. rhamnosus* GG, *L. casei*, and *L. paracasei* as being the most potent inhibitors (192). Cell-free supernatants from *L. rhamnosus* GG cultures had the strongest inhibitory activity, which was attributed to the presence of lactic acid and the peptidoglycan hydrolase major secreted protein 1 (MspI). MspI has chitinase activity, suggesting that *L. rhamnosus* GG uses *C. albicans* cell wall chitin as a substrate to simultaneously enhance its own growth and block *C. albicans* hyphal morphogenesis. Additionally, *L. rhamnosus* GG MspI functions optimally at acidic pH, supporting the synergistic role of lactic acid (192).

In a more recent study, *L. johnsonii* and *B. thetaiotaomicron*, whose populations are significantly reduced during colitis and *Candida* overgrowth, were shown to directly interact with *C. albicans* and induce cell wall degradation (58). More specifically, *L. johnsonii* significantly reduced *C. albicans* growth through its chitinase-like activity, which correlated with improvements in clinical outcomes and restoration of microbial balance in a DSS-induced colitis mouse model challenged with *C. albicans*. Overall, these findings indicate that some *Lactobacillus* species produce hydrolytic enzymes that degrade chitin structures in *C. albicans* cell walls and thus prevent hyphal morphogenesis (Fig. 2).

INTERACTIONS BETWEEN LACTOBACILLI AND *ENTEROCOCCUS FAECALIS*

Mucus-Binding Pili

Broadly speaking, a microbial strain is considered competitive if its activity reduces the fitness of another strain with which it shares resources. Competition between two ecologically stable microbes can result in either domination of one strain, establishment of separate metabolic niches (i.e., a divergence in resource requirements), or separation into distinct "territorial niches" from an originally mixed population (193). Given that *E. faecalis* establishes invasive infection by forming biofilms (wherein adherence to mucus is a necessary first step) and lactobacilli are known to have mucus-binding structures on their surface (194, 195), competition for mucus-binding sites is a potential means by which certain *Lactobacillus* strains inhibit *E. faecalis* pathogenesis.

This possibility was substantiated by a study in which a vancomycin-resistant *Enterococcus* (VRE) strain of *E. faecium* was observed to have increased mucus-binding capacity compared with nonpathogenic enterococci (173). Moreover, the VRE isolate

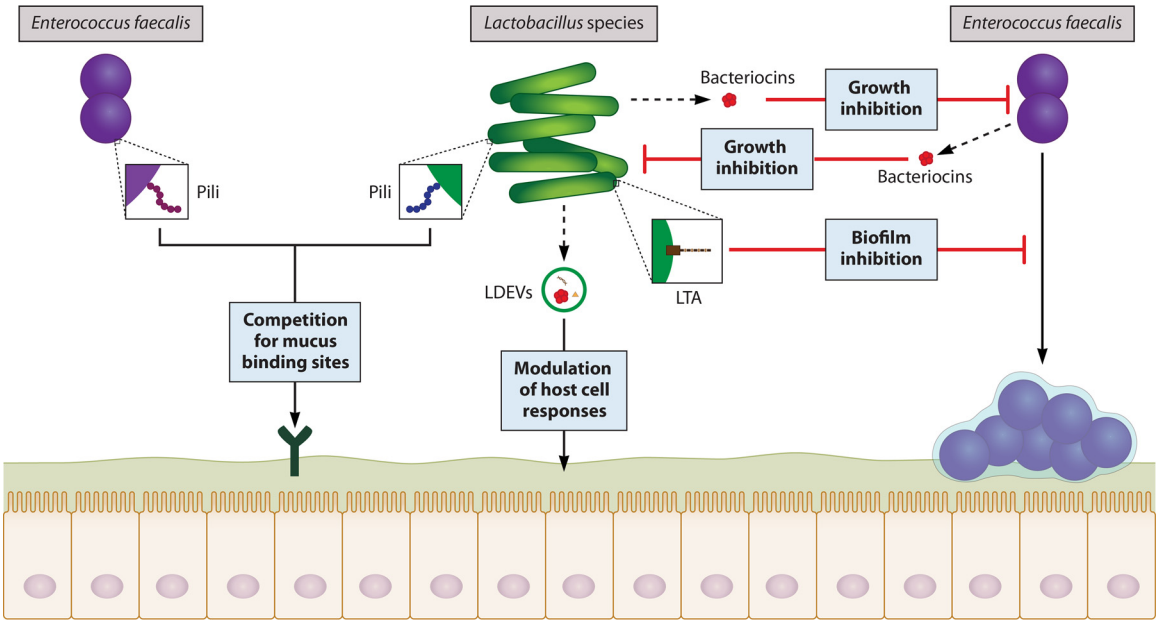

FIG 3 Mechanisms of interaction between *Lactobacillus* species and *E. faecalis*. Lactobacilli and enterococci compete with one another for binding sites along the GI tract via mucus-binding pili on their cell surface. *Lactobacillus* species generally have high-affinity mucus-binding pili and thereby block *E. faecalis* adherence. Initial adherence to host cells is required for the establishment of biofilms, which are associated with enhanced resistance to antimicrobials and host immune responses; thus, competitive exclusion via surface pili can either dampen or facilitate *E. faecalis* pathogenesis, depending on their relative affinity for binding sites. Lipoteichoic acid (LTA) structures found in the cell wall of *Lactobacillus* species are also capable of antagonizing *E. faecalis* biofilm formation and are speculated to achieve this effect by regulating the expression of *E. faecalis* quorum-sensing molecules (QSMs) critical to biofilm formation and integrity. Both lactobacilli and *E. faecalis* produce bacteriocins with antimicrobial activity against the other. The bacteriocin CRL 1238 secreted by vaginal and intestinal *L. salivarius* strains reduces the growth of *E. faecalis*, while the *E. faecalis*-derived bacteriocins enterocin 1071 and enterolysin A target *Lactobacillus* species. Bacteriocins can be secreted on their own or within extracellular vesicles, which offer protection from proteolytic enzymes and can deliver their cargo to more distal sites without triggering an adverse immune response. More specifically, *Lactobacillus*-derived extracellular vesicles (LDEVs) from *L. acidophilus* and *L. plantarum* have been shown to reduce the growth and virulence of *E. faecalis* by delivering bacteriocins to *E. faecalis* and inducing an upregulation of host defense genes.

had undergone mutations such that its pili more closely resembled the mucus-binding SpaCBA pili of *L. rhamnosus* GG, presumably improving its ability to adhere. In the absence of *L. rhamnosus* GG cells, *E. faecium* adherence was significantly reduced by antibodies raised against the mucus-binding domain of SpaCBA, suggesting cross-reactivity between the mucus-binding pili of the two strains. Based on these observations, lactobacilli may normally outcompete enterococci for adherence to the mucus layer and thus prevent biofilm formation and subsequent pathogenesis.

In agreement with these results, administration of *L. rhamnosus* GG to VRE-positive patients has been demonstrated to decrease and even clear VRE colonization in several randomized trials (196, 197). While it should be noted that *E. faecium* and *E. faecalis* strains of VRE have distinct clinical features and likely interact differently with lactobacilli in the GI tract, as members of the genus *Enterococcus*, they have similar requirements for pathogenesis (198). First and foremost, they must bind the mucosal layer in sufficient numbers to form a biofilm whereby they become more resistant to host and microbial defense mechanisms. Competitive exclusion via mucus-binding pili is therefore predicted to be an important strategy used by certain strains of *Lactobacillus* to inhibit *E. faecalis* biofilm formation as well (Fig. 3).

Lipoteichoic Acids

Lipoteichoic acid (LTA) is an important cell wall component unique to Gram-positive bacteria, including lactobacilli and enterococci. There are five different types of LTA which vary in structure and elicit different immune responses following recognition by Toll-like receptors (TLRs) (199). For example, LTA from *Lactobacillus plantarum* weakly stimulates TLR2 and thus poorly induces inflammatory mediators, while LTA

from pathogenic *E. faecalis* acts as a virulence factor and mediates biofilm formation in addition to triggering production of proinflammatory cytokines (200, 201). A study investigating the effects of *L. plantarum* LTA (LpLTA) on the Gram-positive pathogen *Staphylococcus aureus* found that LpLTA interferes with *S. aureus* biofilm formation by inhibiting production of the QSM autoinducer-2 (AI-2). As a result, *S. aureus* had reduced expression of intracellular adhesion (*ica*) locus genes which are essential for synthesis of the major exopolysaccharide component of biofilms (202). *Lactobacillus*-derived LTA is anticipated to have a similar effect on *E. faecalis* biofilms.

Recently, LTAs from several *Lactobacillus* species, including *L. plantarum*, *L. acidophilus*, *L. casei*, and *L. rhamnosus* GG, were found to inhibit *E. faecalis* biofilm formation and even disrupt preformed biofilms (203, 204). Interestingly, although crystal violet staining showed dose-dependent decreases in adherent *E. faecalis* cells after incubation with LTA, the optical density at 600 nm was unchanged. This result implies that *Lactobacillus* LTA does not interfere with *E. faecalis* planktonic growth—only its ability to form biofilms (Fig. 3). Scanning electron microscopy revealed that LpLTA could reduce the size of 3-week-old *E. faecalis* biofilms and also enhance antibiotic-induced biofilm disruption (204). Based on the LpLTA and *S. aureus* data (202), it is likely that LTAs similarly regulate expression of *E. faecalis* QS molecules, such as sortase A and enterococcal surface protein (Esp), which are known to be important for its biofilm formation and integrity (205, 206).

Lactobacillus-Derived Bacteriocins

Bacteriocins are a diverse group of antimicrobial peptides that are produced by bacteria and can provide them with a competitive advantage (207). The rising concern of antibiotic resistance has stimulated an interest in bacteriocins as an alternative and/or supplement to antibiotics, with the notion that physical interference by intact cells might not be required for decolonization of competing bacteria. In particular, many *Lactobacillus* strains are capable of generating a variety of bactericidal agents, including bacteriocins, hydrogen peroxide, and organic acids (208), which could represent interaction mechanisms used by commensal lactobacilli to inhibit pathogens such as *E. faecalis*.

In one study, the *in vitro* antagonistic activity of several *Lactobacillus* strains isolated from curd samples was tested against some common human pathogens (209). Of these lactobacilli, isolates identified as *L. fermentum* had the most potent activity against *E. faecalis*. Treatment of the bacterial supernatants with protease led to a loss of inhibitory activity, but growth inhibition was still observed when supernatants were treated with catalase and organic acid-neutralizing agents, ruling out hydrogen peroxide and organic acids as the relevant antimicrobial products. Although the *Lactobacillus*-derived bacteriocins themselves were not characterized, this study identifies several environmental strains of *Lactobacillus* that produce bacteriocins with inhibitory activity against *E. faecalis*.

Probiotic *Lactobacillus* strains from environmental samples have been the focus of most bacteriocin-related research to date. However, in order to understand the interactions of indigenous lactobacilli with other microbes in the GI tract, it is important to also consider strains derived from mucosal sites. Notably, *L. salivarius* isolated from the human vagina and GI tract have also been shown to antagonize major pathogens, including *E. faecalis*, through the production of several bacteriocins. Of these bacteriocins, CRL 1238 has been shown to specifically inhibit *E. faecalis*, while Abp118 is active against other Gram-positive pathogens such as *Listeria monocytogenes* (210–212). It remains to be determined whether Abp118 targets *E. faecalis* as well. Taken together, these data indicate that bacteriocins from many lactobacilli—either environmental or stable colonizers in the human microbiota—can antagonize *E. faecalis* (Fig. 3).

Enterococcus-Derived Bacteriocins

E. faecalis and other enterococci use pheromone-responsive plasmids (PRPs) to transfer virulence, antibiotic resistance, and bacteriocin genes to other enterococcal cells (213). PRPs facilitate inter- and intraspecies gene transfer, making them likely

contributors to the widespread antibiotic resistance observed in *E. faecalis* and *E. faecium* strains. The ability to transfer bacteriocin genes to other enterococci may be a mechanism by which *E. faecalis* can outcompete lactobacilli and other niche competitors.

pPD1 is an *E. faecalis* PRP system that carries the bacteriocin determinant *bac21* (214). Notably, *E. faecalis* strains harboring pPD1 have resistance to bacteriocin 21 (Bac-21) and are able to outcompete closely related enterococci lacking pPD1 or lacking functional *bac21* within this plasmid in the mouse GI tract (215). Conjugative plasmid-mediated transfer of pPD1 confers resistance to Bac-21 in addition to spreading its genetic material and thus the ability to produce Bac-21. As a result, *E. faecalis* strains lacking pPD1 are sensitive to Bac-21 and displaced from the GI tract. Although Bac-21 was not found to significantly affect levels of lactobacilli in the mouse GI tract, other *E. faecalis* bacteriocins, including plasmid-encoded enterocin 1071 and chromosome-encoded enteroylsin, are active against *Lactobacillus* species (216, 217). *E. faecalis*-derived bacteriocins can therefore impart a competitive advantage over lactobacilli and other enterococci, which likely promotes *E. faecalis* pathogenesis (Fig. 3).

Extracellular Vesicles

Bacterial extracellular vesicles (EVs) are membrane-bound structures that can enclose a variety of proteins, lipids, and nucleic acids and are capable of reshaping the microbial environment. Importantly, they can traverse and be taken up by epithelial cells and thus deliver their cargo to host cells in distal sites to modulate host physiology (218). More specifically, *Lactobacillus*-derived EVs (LDEVs) suppress proinflammatory signaling and enhance expression of tight junction proteins (219) (Fig. 3). Supporting this notion, EVs isolated from gut-associated *L. plantarum* were found to prolong the survival of *C. elegans* worms previously infected with a vancomycin-resistant strain of *E. faecium* (220). While this effect was attributed solely to upregulation of host defense genes in both *C. elegans* and mammalian cells, it is also possible that EVs from this and/or other *Lactobacillus* strains carry bacteriocins to pathogenic enterococci, leading to enhanced protection from infection.

Recently, *L. acidophilus*-derived EVs were found to contain bacteriocins and deliver them to niche competitors by fusing with target cell membranes (221). Considering that the use of bacteriocins as therapeutics for antibiotic-resistant infections has been hampered by a lack of reliable delivery methods, EVs could be a promising solution in that they offer protection from proteolytic enzymes and may not induce adverse immune reactions. Furthermore, bacteriocins derived from lactobacilli have been shown to specifically antagonize *E. faecalis* (209, 212), so although their transportation has not explicitly been characterized, LDEVs are a conceivable mechanism by which *E. faecalis*-targeting bacteriocins can be delivered (Fig. 3).

INTERACTIONS BETWEEN *E. FAECALIS* AND *C. ALBICANS*

Despite them being prominent nosocomial pathogens, the interplay between *C. albicans* and *E. faecalis* in the GI tract is vastly understudied. Consequently, with the exception of a few studies, the mechanisms underlying their interactions have not been explored, much less elucidated. Here, we report what is currently understood on this topic but would like to emphasize that this lack of knowledge should be considered an opportunity for future research, as *C. albicans* and *E. faecalis* each pose significant threats to human health.

Induction of White-Opaque Regulatory Switch

Interactions between *E. faecalis* and *C. albicans* are especially significant due to the fact that they are both opportunistic pathogens that occupy the same niches and are frequently coisolated from polymicrobial infections. *C. albicans* and *E. faecalis* form mixed-species biofilms *in vitro*, making it possible to study their interaction mechanisms. The presence of *E. faecalis* can significantly reduce overall biofilm thickness without affecting the growth of *E. faecalis* itself, suggesting that *E. faecalis* antagonizes

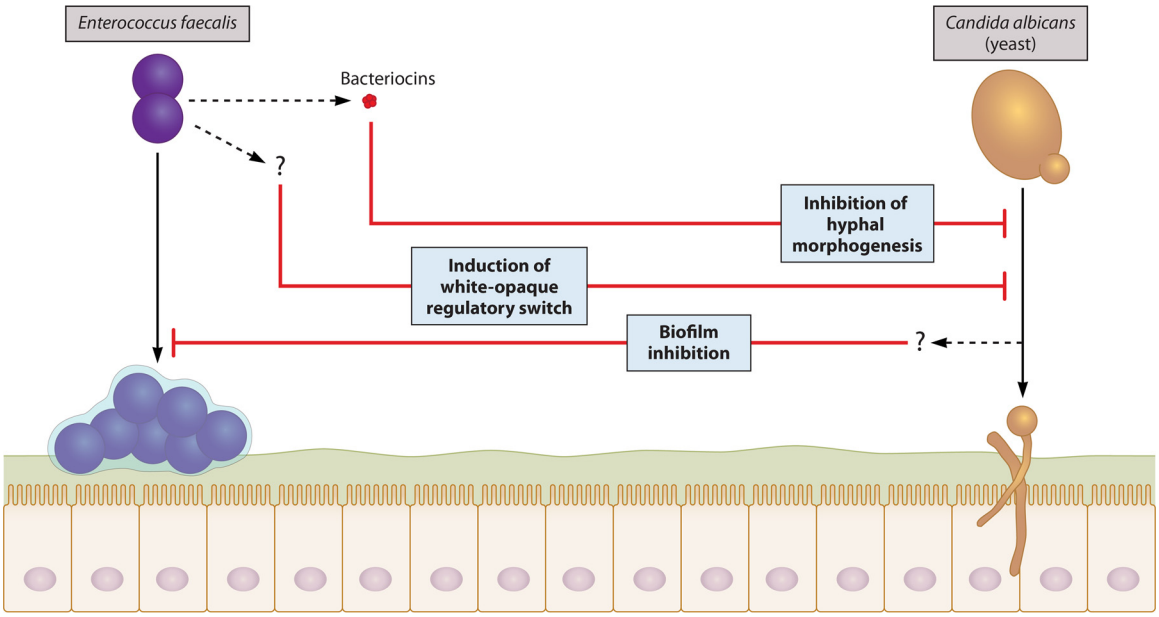

FIG 4 Mechanisms of interaction between *E. faecalis* and *C. albicans*. Interestingly, these two opportunistic pathogens enhance each other's growth but dampen each other's virulence *in vivo*. The mechanisms underlying this unusual interplay are largely unknown and require additional research—particularly in regard to how *C. albicans* interacts with *E. faecalis*. *E. faecalis* induces the upregulation of the white-opaque master regulator WOR1 in *C. albicans*. Notably, other genes involved in the white-opaque regulatory switch are not upregulated by *E. faecalis*, but even partial induction of the less virulent opaque phenotype leads to a significant reduction in *C. albicans* biofilm thickness. The specific signals and pathways involved in this outcome have yet to be determined. A better characterized interaction mechanism involves the production of a bacteriocin by *E. faecalis*. *E. faecalis* uses its Fsr quorum-sensing system not only to regulate its own virulence but also to sense *C. albicans* and release the bacteriocin EntV, which inhibits *C. albicans* hyphal morphogenesis and biofilm formation. It is unclear whether EntV itself is also responsible for the observed reduction in *E. faecalis* virulence or if *C. albicans* produces molecules that suppress *E. faecalis* biofilm formation, either directly or by modulating other cells' activities.

C. albicans biofilm formation (44). Gene expression analysis showed a strong upregulation of the white-opaque master regulator *WOR1* in *C. albicans* cells. The opaque phenotype is less prone to hyphal morphogenesis than the white phenotype under physiological conditions encountered in the GI tract and is therefore generally considered less virulent (222). However, other genes involved in the white-opaque regulatory switch (i.e., *WOR2*, *WOR3*, and *CZF1*) were not upregulated, indicating that *E. faecalis* only partially induces this switch and is therefore more likely repressing white cell formation than promoting a switch to opaque. Nevertheless, these results demonstrate that *E. faecalis* can directly interact with *C. albicans* in biofilms and alter its gene expression to inhibit pathogenesis (Fig. 4).

Enterococcus-Derived Bacteriocins

E. faecalis virulence is regulated by its Fsr QS system. In this system, three genes (*fsrA*, *fsrB*, and *fsrC*) respond to extracellular accumulation of a peptide lactone by producing the proteases gelatinase (GelE) and serine protease (SprE), whose enzymatic activity is required for *E. faecalis* biofilm formation (223). Surprisingly, coinfection with clinical strains of *C. albicans* and *E. faecalis* reduces killing of *C. elegans* nematodes compared with infection with one or the other microbe, indicating that *C. albicans* also suppresses *E. faecalis* virulence *in vivo* (8). In addition to inhibiting *C. albicans* biofilm formation, wild-type *E. faecalis* inhibited hyphal morphogenesis, while mutants lacking functional GelE or SprE did not, confirming the involvement of the Fsr QS system in the interactions of these microbes (8). It was later revealed that *E. faecalis* secretes a bacteriocin called EntV, which is responsible for its inhibition of *C. albicans* hyphal morphogenesis and biofilm formation and that GelE was required for processing into its active form (9, 224). Thus, *E. faecalis* uses the Fsr system to sense *C. albicans* and

produce the bacteriocin EntV, which antagonizes *C. albicans* biofilm formation and filamentation (Fig. 4).

INSIGHTS FROM OTHER *C. ALBICANS* INTERACTING PARTNERS

Mechanistic studies looking at the interactions between *C. albicans* and other bacteria may provide important framework for future research on *C. albicans-Lactobacillus* and *C. albicans-E. faecalis* interaction mechanisms—especially for potential experiments involving targeted gene expression analysis. For example, knowing that QSMs, such as farnesol, and lipid mediators, such as prostaglandins, are involved in some of these interkingdom interactions (225–229), it would be interesting to study the effects of those molecules on *E. faecalis* and *Lactobacillus* species as well as on host cells.

Quorum-Sensing Molecules and Prostaglandins

Interactions with *Pseudomonas aeruginosa*. In addition to modulating phenotypic switching in response to cell density, the QSM farnesol promotes *C. albicans* survival in the presence of *Pseudomonas aeruginosa*. Like *E. faecalis*, *P. aeruginosa* is an opportunistic bacterial pathogen that is commonly found in mixed-species infections with *C. albicans*—particularly in the lungs of cystic fibrosis patients (230). However, unlike *E. faecalis*, it can antagonize the overall growth of *C. albicans* in addition to its virulence (231, 232). Specifically, *P. aeruginosa* uses an *N*-acyl homoserine lactone (AHL)-dependent QS system to attach to and kill *C. albicans* hyphae (225). 3-Oxododecanoyl-homoserine lactone (3-oxo-HSL) is a QSM produced by this system that mediates *P. aeruginosa* adherence to *C. albicans* hyphae by triggering the synthesis of surface adherence proteins (225). Once adhered, redox-active phenazines also produced by the QS system can directly kill *C. albicans* cells by generating reactive oxygen species (ROS) and reducing cAMP levels (225). In doing so, *P. aeruginosa* undermines *C. albicans* cell wall integrity and blocks hyphal morphogenesis. However, farnesol produced by *C. albicans* prevents the formation of hyphae and thereby protects against killing by *P. aeruginosa* (225, 233). During infection, both release arachidonic acid, which they can transform into eicosanoids (234). Farnesol also promotes the production of phenazines by *P. aeruginosa*, which are toxic to a variety of bacteria and may therefore enable *C. albicans* to indirectly outcompete other bacteria (229). The production of farnesol is also important for *C. albicans* dissemination, as it has been shown to promote the recruitment of circulating macrophages, which *C. albicans* can kill after being engulfed and transported into the bloodstream (229, 235).

While it remains to be determined whether such QSMs play a role in its interactions with *E. faecalis* and/or *Lactobacillus* species, QS systems are potential mechanisms by which *C. albicans*, *E. faecalis*, and lactobacilli adapt to and antagonize one another. It is likely that QSMs are at least partially responsible for the reduced virulence of *C. albicans* in the presence of these bacteria, as well as the reduced virulence of *E. faecalis* in the presence of *C. albicans* (Fig. 5).

Interactions with *Streptococcus gordonii*. QSMs are also implicated in the interplay between *C. albicans* and *S. gordonii*—another bacterium commonly found in *C. albicans* biofilms (229). The physical interaction of these microbes is mediated by the antigen I/II (AgI/II) polypeptides SspA and SspB expressed on the cell wall of *S. gordonii*. Following bacterial attachment to the mucosa, *C. albicans* binds these polypeptides and coaggregates with *S. gordonii*, enabling proximal cell-to-cell communication via secreted signals (236). These two microbes ultimately enhance each other's persistence through mutualistic interactions; metabolic by-products released by *S. gordonii* can be used as a carbon source by *C. albicans*, and in turn, *C. albicans* biofilms provide an anoxic niche and nutrient source for *S. gordonii* (229, 236). Unlike *E. faecalis*, however, *S. gordonii* also promotes *C. albicans* virulence by abrogating farnesol-mediated inhibition of hyphal morphogenesis, likely via the protein kinase A (PKA) pathway (236).

Interactions with *Staphylococcus aureus*. Similar to *S. gordonii*, the presence of *S. aureus* in *C. albicans* biofilms portends increased mortality compared with monoinfection with either microbe but can also enhance the resistance of both species to

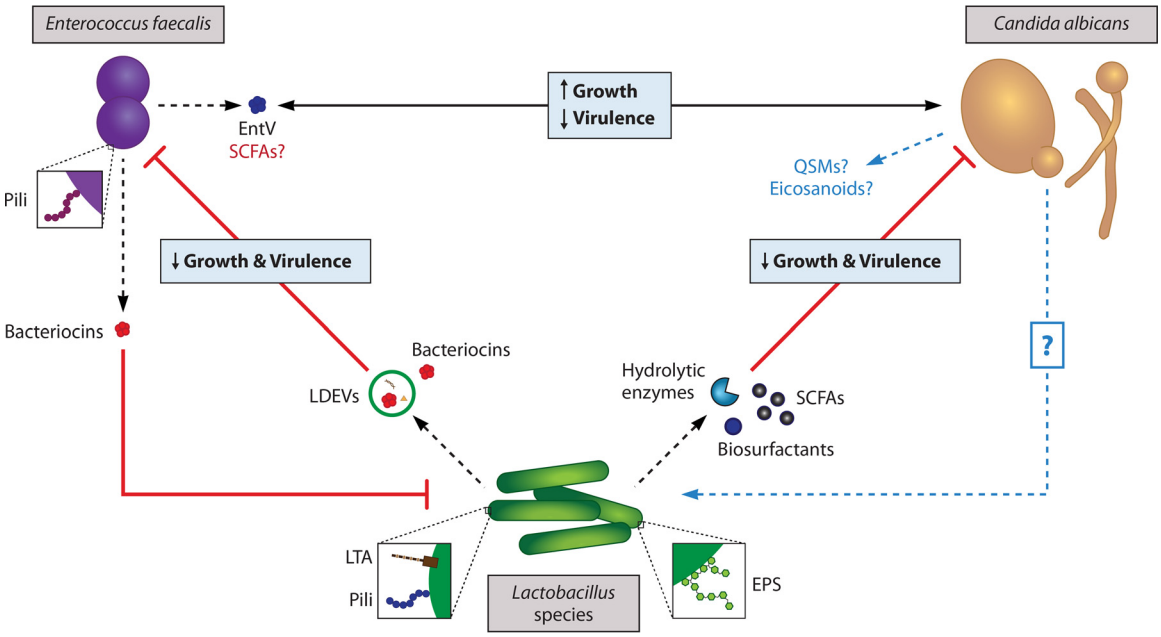

FIG 5 Model of the interplay between *C. albicans*, *E. faecalis*, and various *Lactobacillus* species in the human GI tract. Lactobacilli use a combination of surface and secreted molecules to reduce the growth and virulence of both *C. albicans* and *E. faecalis*. In turn, *E. faecalis* can antagonize lactobacilli via competitive exclusion and/or *Lactobacillus*-targeting bacteriocins. *E. faecalis* and *C. albicans* promote each other's growth but reduce each other's virulence. The bacteriocin EntV produced via the *E. faecalis* Fsr QS system is the only identified molecule mediating this interaction; however, *E. faecalis* has also been shown to suppress the *C. albicans* white cell phenotype, which is more virulent under physiological conditions. Additionally, given that SCFAs produced by lactobacilli have been shown to reduce *C. albicans* hyphal morphogenesis, it is possible that *E. faecalis*-derived SCFAs have a similar effect on *C. albicans*. The overall impact of *C. albicans* on the growth of lactobacilli, as well as the molecules and pathways involved in its interactions with *E. faecalis* and *Lactobacillus* species, have not yet been elucidated. Studies on the interactions of *C. albicans* with *P. aeruginosa*, *S. gordonii*, and *S. aureus* lead us to postulate that *C. albicans* QSMs may underlie its ability to suppress *E. faecalis* virulence. Another possibility is the production of immunomodulatory eicosanoids such as PGE_2, which, by reshaping the immunological landscape, may help *C. albicans* evade the antagonistic effects of LAB and create a more conducive environment for its own growth as well as the growth of *E. faecalis*.

antimicrobial agents (229). In particular, farnesol secreted by *C. albicans* has been shown to increase the tolerance of *S. aureus* to the antibiotic vancomycin by inducing upregulation of efflux pump genes (227), although higher concentrations of farnesol may actually reduce *S. aureus* viability and biofilm formation (226). Furthermore, repeated exposure to farnesol results in the loss of staphyloxanthin, an important *S. aureus* virulence factor (237). However, other studies have noted that mixed-species infections involving these two microbes are associated with higher mortality rates due to induction of the *agr* QS system in *S. aureus*, which leads to increased hemolytic activity as well as production of alpha and delta toxin (238). In any case, interactions between *C. albicans* and *S. aureus* can dramatically alter the growth and virulence of both species in a host. A significant increase in PGE_2 release by *C. albicans* and host cells has been observed in mixed-species infections involving *C. albicans* and *S. aureus*, with PGE_2 promoting *S. aureus* biofilm growth in a dose-dependent manner (228).

Given these observations, it is conceivable that farnesol and *C. albicans*-derived PGE_2 alter the activity of *E. faecalis* and *Lactobacillus* species either directly or by altering the immunological landscape (Fig. 5), although this possibility has not yet been investigated.

CONCLUDING REMARKS

C. albicans and *E. faecalis* are two microbiologically and clinically distinct microbes that are both common gastrointestinal commensals and opportunistic pathogens (i.e., "pathobionts" [239, 240]) but have emerged as important clinical challenges in the modern acute care setting. Despite their clinical co-occurrence, their biological interactions are understudied and represent significant knowledge gaps. These gaps are unfortunate

as both *C. albicans* and *E. faecalis* are poised to become yet more dangerous with invasive medical procedures becoming increasingly common. Additionally, both taxa are precariously close to antibiotic resistance crises with few options for each. Thus, an understanding of the factors that facilitate the colonization and persistence of these organisms provides an opportunity to intervene before they cause harm. Such is the potential role of various *Lactobacillus* species, whose colonization of mucosal surfaces antagonizes these pathobionts and augments protective mucosal immunity.

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