“Candida Albicans Interactions With The Host: Crossing The Intestinal Epithelial Barrier”

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ABSTRACT
Formerly a commensal organism of the mucosal surfaces of most healthy individuals, Candida albicans is an opportunistic pathogen that causes infections ranging from superficial to the more life-threatening disseminated infections, especially in the ever-growing population of vulnerable patients in the hospital setting. In these situations, the fungus takes advantage of its host following a disturbance in the host defense system and/or the mucosal microbiota. Overwhelming evidence suggests that the gastrointestinal tract is the main source of disseminated C. albicans infections. Major risk factors for disseminated candidiasis include damage to the mucosal intestinal barrier, immune dysfunction, and dysbiosis of the resident microbiota. A better understanding of C. albicans’ interaction with the intestinal epithelial barrier will be useful for designing future therapies to avoid systemic candidiasis. In this review, we provide an overview of the current knowledge regarding the mechanisms of pathogenicity that allow the fungus to reach and translocate the gut barrier.

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Introduction

The importance of the intestinal mucosa in the interaction of candida sp. with its host

Formerly described as a harmless commensal of the human mucosal surfaces, C. albicans is also an opportunistic fungus responsible for candidiasis that can range from superficial to invasive and life-threatening infections in debilitated patients, mostly occurring in the hospital setting. Thus, systemic candidiasis is associated with a high crude mortality ranging from 20 to 49%, and almost all of the organs can be secondarily infected following the hematogenous dissemination of the fungus. From a pathophysiological point of view, invasive candidiasis has various stages where C. albicans has to: (i) enter the bloodstream, (ii) survive in the blood reservoir and (iii) escape from the bloodstream in order to establish deep-seated infections.

In the first stages, a clear association between the presence of C. albicans on mucosal surfaces such as the mouth or the vagina and its translocation into the blood has not been established yet. However, various observations strongly suggest that invasive candidiasis are mostly of endogenous origin with the gastrointestinal (GI) tract being the main portal of entry into the bloodstream. Indeed, molecular typing studies have pointed to gut mycobiota as the main origin of disseminating C. albicans isolates in the blood.

On the host side, immune dysfunction such as neutropenia, damage to the mucosal barrier and dysbiosis of the bacterial microbiota have been identified as major risk factors for invasive candidiasis. With in vivo investigations, Koh demonstrated a strong association between (i) dysbiosis of the bacterial microbiota, (ii) mechanical alteration of the gut barrier function, (iii) a decrease in the function of neutrophils (PMNs) and (iv) major risks for systemic candidiasis.

In addition to the role of C. albicans as a commensal or a pathogen and with the advance of Next Generation Sequencing (NGS) for microbiome analysis, recent reports suggest that changes in the fungal microbiota of the gut are linked to the pathogenesis of multiple gastrointestinal (e.g. inflammatory bowel diseases (IBD)) or extra-intestinal disorders (e.g. allergic airway diseases, neurologic disorders, cancer), in which, an increase of colonization by fungal species, including C. albicans, was reported compared to healthy subjects.

All in all, C. albicans is a versatile yeast able to interact with the gut content of its human host both as a commensal, a pathogen or a major colonizer of the GI tract. This transition from commensalism to pathogenicity involves both host-related factors (e.g. environment of the digestive tract, the gut mucosa, genetics and health status), the microbiota (i.e. dysbiosis), and C. albicans itself. In this context, the purpose of this review is to discuss the interaction between C. albicans and the intestinal epithelial barrier.

Interaction of microorganisms with the intestinal mucosa

Intestinal factors influencing the interaction of micro-organisms with the gut mucosa

Human intestinal microbiota and mycobiota

The human intestinal microbiota is a complex ecosystem, largely dominated by bacteria in terms of number (i.e. around 10^{14} bacterial cells) and species diversity (500 to 1000 species, mainly anaerobes). However, the global gut microbiota also comprises archaea, viruses and eukariota such as parasites and fungi. Whereas the precise contribution of gut-associated archaea, viruses and parasites in human physiology remains to be specified, research over the last few decades has given us a more comprehensive view of the contribution of bacteria and fungi to gut-associated microbiota (GM) and the potential impact on human health.

In healthy adults, the composition of the GM is unique to each individual. It differs along the digestive tract and varies according to environmental and lifestyle stimuli.

Although specialized in the digestion of nutrients, the GM contributes to the host’s gut homeostasis by (i) modulating the host’s energy metabolism, (ii) sustaining gut integrity, (iii) preventing gut colonization by pathogens and (iv) promoting the development and maturation of...
the gut-associated immune system.\textsuperscript{26,27} Consequently, an imbalanced GM composition can result in the dysregulation of host homeostasis contributing to the onset or progression of many diseases. Indeed, dysbiosis of the GM is associated with the pathogenesis of intestinal (e.g. IBD, irritable bowel syndrome, coeliac disease) but also extra-intestinal diseases (e.g. allergy, asthma, disruption of the immune system, metabolic diseases, cardiovascular diseases, and neurologic diseases).\textsuperscript{-28–32}

Among microbiota components, fungi account for about a quarter of the species diversity but for less than 0.1% of the GM in quantity.\textsuperscript{7} The human mycobiota comprises 158 genera and 390 species among which only 221 are found in the digestive tract.\textsuperscript{7} However, despite growing interest in the gut mycobiota, several issues remain to be addressed regarding its precise composition from one individual to another. The most commonly-detected fungi in the human GM (in order of frequency) are the genera \textit{Candida}, \textit{Malassezia}, \textit{Aspergillus}, \textit{Debaryomyces}, \textit{Penicillium}, \textit{Cladosporium}, \textit{Trichosporon}, \textit{Galactomyces}, \textit{Saccharomyces} and \textit{Cryptococcus} (i.e. the percentage of positive samples reported in gut mycobiome studies being 80, 25, 24, 21, 20, 18, 9, 9, 6 and 4% respectively).\textsuperscript{33}

However, the mycobiota appears less stable than the bacterial microbiota and highly subject to changes brought on by environmental factors, particularly diet (e.g. animal-based versus plant-based diet).\textsuperscript{33} Although, the role of fungi in the human GM remains poorly understood, recent studies have highlighted the role of diverse fungal communities in host physiology. Symbiotic relationships between fungi inhabiting the human GI tract and the host have indeed been reported to be essential for digestion functions.\textsuperscript{34} Additionally, other findings have underscored the relationship between the gut mycobiota and human diseases. Associations between the mycobiome biodiversity in IBD or in obesity, and gut environment modifications have been reported.\textsuperscript{15,35} For example, Mar Rodriguez \textit{et al.} observed differences in the biodiversity of the mycobiome of obese compared to healthy individuals, suggesting that this fungal dysbiosis contributes to changes in the lipid and glucose metabolisms observed in diabetic patients.\textsuperscript{35} Finally, antifungal or antibiotic treatments can also lead to microbial dysbiosis and so to a disruption in the balance between bacterial and fungal communities, highlighting the interdependence of fungi and bacteria in the gut.\textsuperscript{17}

**Intestinal Epithelial Cells (IECs)**

The intestinal epithelium (IE) consists of a monolayer of cells covering a surface of $\sim 400 \text{ m}^2$, organized into crypts and villi. Pluripotent intestinal epithelial stem cells residing in the bottom of the crypts ensure a continuous renewal of the IE, where the local environment drives their proliferation and functional differentiation. IE encompass differentiated cell types grouped under the term intestinal epithelial cells (IECs) (\textit{i.e.} enterocytes, enteroendocrine cells, goblet cells, Paneth cells, Microfold (M) cells and Tuft cells) with specialized functions (\textit{i.e.} absorption, hormone secretion, mucus secretion, antimicrobial peptide (AMPs) production, antigen sampling and taste-chemosensory responses respectively) in addition to Cup cells whose function remains to be specified.\textsuperscript{36} Additionally, IECs exert immunoregulatory functions that are critical for the development, maturation and homeostasis of the immune system all along the gut mucosa. Finally, thanks to this complex system of cells and functions, IECs form a physical and biochemical barrier capable of segregating microorganisms from the host with the ability to discriminate commensals from pathogenic microorganisms. IECs respond differentially to commensal or pathogenic microbial signals that consequently reinforce or weaken their barrier function. In parallel, the mucosal biochemical and immune systems orchestrate appropriate immune responses to these microbial signals that can range from the tolerance of commensal microorganisms to anti-pathogenic responses.\textsuperscript{37}

**Physical barrier function.** IECs are mostly composed of enterocytes (over 80%) that form a monolayer of differentiated and polarized epithelial cells with an apical side that displays microvilli which form the brush border exposed to the digestive lumen.\textsuperscript{38} Beyond their role in nutrient and fluid absorption, enterocytes also contribute to the integrity and impermeability of the IE by establishing the intestinal border. They form a
physical barrier between the content of the gut lumen and the underlying tissues, limiting the translocation of microbes and their related products. Thus, the cohesion of the IE relies particularly on junctional intercellular complexes including tight-junctions (TJs) and weak junctions (i.e. adherens-, gap-junctions and desmosomes) (Figure 1). The composition and functions of these junctional complexes vary by IEC type, especially for TJs, but their structural organization has been extensively studied in enterocytes (Figure 1). Between enterocytes, adherens junctions (AJs) contribute to cell-cell adhesion and intracellular signaling whereas gap-junctions and desmosomes participate in cell-cell communication and adhesion, respectively. Together with AJ, TJs form a seal (i.e. the apical junctional complex) that ensures the architectural cohesion and integrity of the IE. This complex is closely linked to the cytoskeleton that is crucial in maintaining the cohesion and structure of the IECs by extending throughout the cytosol (Figure 1). Finally, TJs, the most apically located intercellular junctions, are crucial for the IE’s role of physical barrier since they are targeted by numerous physical and chemical factors, including cytokines, proteases, hormones, neurotransmitters, dietary components, bacterial and fungal toxins, and xenobiotics that can alter TJs and consequently modulate the permeability and integrity of the IE. Commensal bacteria can modulate impermeability and integrity in a homeostatic manner by targeting TJs, whereas enteric pathogens including bacteria, viruses, parasites and possibly fungi have developed strategies aimed at exploiting TJs to promote their invasiveness into IECs.

**Secretory functions of IECs.** IECs also express secretory functions reinforcing the physical barrier role of the epithelial layer and ensuring biochemical functions.

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**Figure 1.** The intercellular junctions between enterocytes at the digestive barrier.
(A) Composition and organization of the enterocyte-enterocyte junctions in the intestinal epithelium. Tight junctions (or TJs) are the first intercellular junctions present at the apico-lateral region of enterocytes followed by the adherens junctions (AJs), the desmosomes and finally the GAP junctions at the baso-lateral region. (B) Composition and organization of the TJs and AJs. The TJs and the AJs form circumferential junctions composed by transmembranous proteins, including Claudins, TJ associated Marvel domain containing Occludin, Tricellulin and Marvel D3, and JAMs for TJs and E-cadherin and Nectin for AJs, all connected to the cytoskeleton through various proteins (i.e. Zonula Occludens (ZO1-3) proteins, Cinguline, Catenin and Afadin).
First, enterocytes secrete the glycocalix that mainly contains transmembrane mucin glycoproteins covering the apical dense microvilli surface, which locally protects the enterocyte cell membranes. Moreover, the IE is lined with an αββ (Angiogenin 4) ability to trap and secrete cytokines (IL-82) through the stimulation of specific PCs that reside exclusively at the base of the crypts in the small intestine of healthy individuals (Figure 2). These specialized cells contain granules whose secretion is modulated, among others, by microbes and microbial products75,76 through the stimulation of specific Pattern Recognition Receptors (PRRs) located at the surface of IECs. These granules are mostly enriched in antimicrobial peptides (AMPs) including α- and β-defensins, lysozyme C,79 secretory group IIA phospholipase A2 (sPLA2),80 Regenerating Islet-Derived 3 Gamma (REG3γ),81 α-1 antitrypsin,82 Angiogenin 4 and Cathelicidin.84 PCs also release cytokines (IL-17A, TNF-α, IFN-β and IL-1), proteases (Metalloprotease 7), proteins and scaffolding molecules as well as non-granule molecules including Wnt proteins, Epidermal Growth Factor and Notch ligands.82 These non-granule secretions create a specific microenvironment called the “stem cell niche”, that surround the stem cells and is essential for the regeneration and differentiation of specific IECs in the small intestine.82,85

Additional secreted antimicrobial factors are found in the intestinal mucus layers, including secretory Immunoglobulin A (sIgA). sIgA are secreted by IgA+ B cells moving from the germinal center of Peyer’s patches to the lamina propria in intestinal villi. They provide an adaptive immune component which is crucial for maintaining gut homeostasis by (i) inhibiting microbial motility and improving the mucus’ ability to trap microorganisms, (ii) clearing the microorganisms through peristalsis or mucociliary exclusion, (iii) shaping and maintaining the GM composition and (iv) neutralizing the bacterial toxins.90,91

Furthermore, IECs constitutively produce a panel of cytokines, including TGF-α, IL-10, IL-15, and IL-18, that are crucial for the basal recruitment of immune cells, the regulation of IEC growth and so gut homeostasis.22–95 These cytokines also up-regulate the production of other cytokines (i.e. IL-1α or β, IL-6, IL-7, IL-8, TNF-α and TGF- β) and/or chemokines by immune cells during microbial infection.92,96–98

Finally, bacterially derived antimicrobial factors, among them the peptides called bacteriocins, are secreted by gram-positive and gram-negative bacteria in the intestinal mucus layer. These bacteriocins have a restrained antimicrobial activity...
The gastro-intestinal tract forms a physical and biochemical barrier capable of segregating microorganisms from the host with the ability to discriminate commensals from pathogenic microorganisms. The physical barrier consists of a monolayer of cells, which includes various intestinal epithelial cell types (IECs) differently organized from the small intestine to the colon. The biochemical barrier consists of a mucus layer whose composition, structure and properties differ between the small intestine and the colon. In the small intestine, the mucus is composed of a highly dynamic monolayer, not anchored to the surface of the epithelial cells. This monolayer of mucus is permeable to the bacteria. However, the distal peristaltic movements keep the microorganisms away from the surface of the epithelial cells. In the colon, the mucus is organized in two layers: the inner layer and the outer layer. The inner layer is in perpetual renewal (approximately every 1 to 2 hours) in order to remain totally germ-free. This layer is firmly anchored to the epithelial barrier through the interaction between mucins in the mucus and the mucins-binding protein located at the surface of the epithelial cells. Due to its size-exclusion filter function, the inner layer of mucus is impermeable to microorganisms. Finally, the outer layer is the normal habitat of intestinal commensal microbiota. In addition to the secretion of bioactive molecules such as nutrients, hormones, neuropeptides, cytokines and lipids in the gut lumen, the gut microbiota takes an active part in this permanent remodeling as highlighted in germ-free animals in which a thinner layer of mucus is observed as the result of a decreased number of goblet cells compared with conventional animals. The outer-most layer of mucus is a reservoir of dense populations of commensal microorganisms whose composition is linked to the existing luminal populations. Consequently, normal or altered GM and mycobiota will influence goblet cell function as well as the composition and volume of the mucus layer by mechanisms probably involving both the direct effect of locally released microbial factors and/or the indirect effect of bioactive or immune factors resulting from the host-response to intestinal microbes. Moreover, the mucus layer is also a biochemical barrier thanks to the presence of various secreted antimicrobial factors mostly secreted by the cytoplasmic granule-rich Paneth cells (PCs). These PCs are located at the base of the small intestinal crypt in healthy individuals. Various factors, including cholinergic agonists, bacteria and bacterial products (such as lipopolysaccharides and lipoteichoic acid), lead to the discharge of PC granules from the crypt into the mucus layer, forming a biochemical barrier that is crucial for establishing baseline homeostasis for mucosal and systemic inflammatory response. The PCs mainly secrete a panel of antimicrobial peptides (AMPs), which are released in intestinal mucus layer in the small intestine in humans. The composition of the mucus changes along the GI tract, contributing to the increase of the amount of microorganisms in the digestive microbiota between the small intestine and the colon.
spectrum that affects the composition of the microbiota (interdependency within bacterial communities).\textsuperscript{74} Moreover, the gut microbiota produce several metabolites (from anaerobic fermentation of exogenous undigested dietary components) such as short-chain fatty acids (SCFAs), aryl-hydrocarbon receptor ligands or polyamines, which interact with host cells and thus influence immune response.\textsuperscript{99} Altogether, the small intestine is constantly exposed to bacteria and bacterial products, which explains the constant baseline level of secreted antimicrobial factors in the mucus layer.\textsuperscript{100,101}

**Gut mucosal immunity**

IECs play a central role in the intestinal immune response, acting as frontline sensors between GM and the immunity of the gut mucosa.\textsuperscript{96} A close relationship exists indeed between the digestive microbiota and the intestinal mucosa, mediated by a complex intestinal immune system. This mucosal immune system (or MIS) is divided into three physically distinct parts: (i) the intestinal epithelial barrier, (ii) the lamina propria (LP) and (iii) the gut-associated lymphoid tissue or GALT, comprising Peyer's patches (or PPs), isolated lymphoid follicles (or ILF) and mesenteric lymph nodes (or MLNs). Functionally, the intestinal MIS comprises two immune sites, (i) the effector and (ii) the inductive site\textsuperscript{102} (Figure 3). They are challenged with discriminating entero-pathogenic microorganisms from the resident commensal flora, and adapting the immune response as needed, from tolerance to inflammation.\textsuperscript{103} These aspects have been extensively addressed elsewhere\textsuperscript{27} and will not be developed in this review. However, the specialized cells of the immune system are of particular interest in the context of this review because they contribute to the translocation of micro-organisms through the gut barrier.

In this context, an important effector site of gut mucosal immunity is the lamina propria layer, which has the key functions of (i) preventing entry/spread of pathogens across gut mucosa and (ii) destroying invasive pathogens.\textsuperscript{102} Indeed, almost all of the intestinal immune cells are found in the LP layer; this includes innate immune cells (including dendritic cells (DCs), macrophages (Mφ), Mucosal-associated invariant T cells (MAIT), mast cells and innate lymphoid cells), and adaptive immune cells (Lymphoid T cells and plasma cells).\textsuperscript{104} These immune cells have a crucial function in the interaction with the GM. Among them, the γδ intraepithelial T lymphocytes (that represents the major T cell population within the intestine) respond directly to microbiota signals to promote intestinal homeostasis which (i) helps preserve the integrity of damaged epithelial surfaces\textsuperscript{105} and (ii) produces innate antimicrobial factors and pro-inflammatory cytokines and chemokines in response to resident bacteria that penetrate the intestinal epithelium and to

![Figure 3. Organization and function of gut mucosal immunity.](image-url)
Another important line of immune cells for maintaining intestinal homeostasis are the CD4 regulatory T cells (Tregs). Indeed, Tregs are important response modulators to gut microbiota, notably through the secretion of anti-inflammatory cytokines such as IL-10, which trigger an immunosuppressive response and gut homeostasis. In parallel, the innate lymphoid cells (ILCs) contribute to host defense and immune homeostasis within GALT. Thus, ILCs are able to rapidly respond to gut microbiota contributing to GALT formation and function (Reviewed in 112).

Among GALT, PPs consist of dome-like structures or sub-epithelial domes (SED) containing large B cells follicles and smaller T cells areas, in addition to migratory dendritic cells (DCs) and macrophages (Mφ). These SED are separated from the gut lumen by a single epithelial layer called the Follicle-Associated Epithelium or FAE. The FAE contains epithelial cells, including microfold (M) cells. When compared to the adjacent enterocytes, these M cells display reduced irregular microvilli (short fold-like invagination or microfold) on the apical surface. Moreover, M cells express various apical receptors (e.g. integrin β-1, GP2, C5a and poliovirus receptors) that serve as a portal of entry for luminal components. At the basolateral membrane, M cells present a large pocket-like invagination that contains B lymphocytes (LB) and T lymphocytes (LT) in equal proportions, Mφ and DCs. This particular structure in the M cells act as antigen-presenting cells, sampling gut luminal antigens, macromolecules and microorganisms present in the intestinal lumen in different ways (i.e. transcytosis, phagocytosis, microvesicle shedding) without any degradation. Consequently, the translocation of antigens through M cells is pivotal for linking the contents of the gut to the immune system, with the aim to trigger an appropriate immune response to the harmless or harmful stimuli in the gut lumen. In a healthy host, this process largely contributes to the tolerance toward antigens derived from diet or the commensal flora through signaling pathways involving an Ets (E-twenty-six-specific sequence) transcription factor, SpiB, which acts as a major regulator of the structural and functional maturation of M cells.

On the contrary, many pathogenic microorganisms including reoviruses, polioviruses, and enteric bacteria (e.g. Salmonella typhimurium, Shigella flexneri, Yersina enterocolitica) have developed strategies to exploit (i) weaknesses in the cell-cell junctions bordering M cells and (ii) the absence of mucus covering these specific cells. Consequently, M cells form a possible “gateway” that allow pathogens to enter and invade the host, triggering deleterious immune responses.

**Candida albicans’ interaction with the intestinal barrier**

*C. albicans* is an opportunistic pathogen that interacts dynamically with its human host. Indeed, when colonizing diverse mucosal surfaces of the human host as a commensal, *C. albicans*’ extensive phenotypic plasticity makes it capable of causing life-threatening systemic infections. It is a polymorphic fungus that exhibits *in vivo* yeast or hyphal (and possibly chlamydospore) forms, and the ability to transition from one to another is considered a virulence trait of the fungus. It also expresses metabolic flexibility that largely contributes to its adaptability and virulence to diverse host niches. This phenotypic plasticity is best exemplified by the white and opaque phenotypes that correspond to distinct morphological states of the same isolate able to undergo heritable and reversible epigenetic transitions. In addition, this phenotypic and metabolic flexibility allow the fungus to adapt to specific fluctuating external stresses, including nutrient conditions, temperature and pH. These stresses drive the switch of *C. albicans* to the white or opaque state, each displaying specific biological features affecting, among others, mating competency, immunogenicity, virulence and niche specificity. While white cells are the most clinically relevant form of *C. albicans* and considered as an all-around phenotype fitting various environmental conditions, opaque cells correspond to a more metabolically specialized form of the fungus.

The gut environment forms a specific niche characterized by a number of environmental...
factors including pH, temperature, hypoxia, and the presence of serum or carbon sources. There are also a wide range of microbial and nutrient metabolites that can influence morphological changes in *C. albicans* and the phenotype of the fungus. Interestingly, Pande K et al. observed a morphological switch to a “dark” phenotype in *C. albicans* cells exposed to the mammalian gut environment. Indeed, when the Wor1 transcription factor is necessary and sufficient to drive the switch from the white to the opaque state, WOR1 overexpression triggered the switch to a Gastrointestinally-Induced Transition (GUT) morphotype optimized to the gut living in a commensal state. Finally, the gut niche appears to be a complex environment capable of driving alternative phenotype switches that promote commensalism or pathogenicity in *C. albicans* as the result of specific combinations of environmental stresses. However, how and which variations of the gut environment favor the commensal or virulent form of *C. albicans* remain to be specified. Thus, the passage of *C. albicans* through the gut mucosal barrier is a complex process depending on host characteristics that are both extrinsic and intrinsic, associating phenotypic switches that promote *C. albicans* commensalism or pathogenesis.

Notably, the pathophysiology of candidiasis is intimately linked to the ability of *C. albicans* to adhere to and invade host cell barriers. During these processes, *C. albicans* has to face different components of the gut mucosal barrier, including the antimicrobial peptide armory and the mucus layer, to successfully reach and then invade the epithelial layer lining the gut mucosa, possibly resulting in blood dissemination.

**Interaction of *C. albicans* with the gut microbiota**

In the digestive tract, 221 fungal species are part of the microbiota, mostly yeast and filamentous fungi belonging to the Ascomycota, Basidiomycota and Zygomycota phyla. In healthy humans, this mycobiont encompasses almost 66 genera of fungi, mainly including *Saccharomyces* and *Candida* species.

The equilibrium of the healthy microbiome is under the control of transkingdom interactions between the different inhabitants of the microbiota. Among them, bacterial-fungal interactions are particularly important for the homeostatic state, as highlighted by Iliev et al. who reported the existence of mixed fungal-bacterial biofilms in the GI tract of mice. Fungal-bacterial interactions create a complex balance between synergism (e.g. *C. albicans*/*Streptococcus* sp.) and/or antagonism (e.g. *C. albicans*/*Lactobacillus* sp.) pathways, leading to a state of harmony within the microbiota (reviewed in Wang et al., 2014). In this context, the GI microbiota exerts anti-Candidal properties through different mechanisms. Indeed, the bacterial microbiota can modulate *C. albicans* colonization through the production of bacterial metabolites that limits fungal proliferation and virulence. Such bacterial metabolites exert antifungal activities in vitro through molecular mechanisms involving the *C. albicans*’ TOR pathway, a central signaling pathway that controls cell growth in response to environmental nutrient signals in eukariota. For instance, *Lactobacillus* sp. limits *C. albicans*’ growth and virulence, affecting the germ-tube formation in the GI tract through the production of H2O2, organic acids and short chain fatty acids (SCFAs). Thus, bacterial metabolites inhibit *C. albicans*’ hyphal growth and invasion of human enterocytes by repressing the yeast-to-hyphae transition as well as the inducibility of hyphae specific transcripts. In addition, other metabolic products, including dietary products such as tryptophan, exert antifungal activities by enhancing the mucosal reactivity to *C. albicans*. Indeed, tryptophan promotes the local transcription of a bacterial gene that triggers IL-22 productive cells and the proliferation of IL-22-producing innate lymphoid cells in the GI tract. As a result of its pivotal role in innate antifungal resistance, the resulting increased production of IL-22 promotes resistance to colonization by *C. albicans* by attenuating inflammation in the IECs and damage caused by *C. albicans*. As a consequence, disturbances in the bacterial community (or dysbiosis) are associated with enhanced *C. albicans* colonization, as...
reported early in the 1970’s. These observations were underscored in germ-free mice that experienced an increase in colonization as the result of the lack of a bacterial microbiota. Various iatrogenic factors including antimicrobial and immunosuppressive therapies have been reported for their capacity to disrupt the GI microbiota, thus modulating C. albicans colonization. Fan et al. showed that antibiotics specifically targeting anaerobic bacteria, Bacteroidetes and Firmicutes, favored colonization of C. albicans in the gut of mice. These authors observed that anaerobic bacteria from mature adult microbiota were critical for maintaining resistance to C. albicans since Bacteroides thetaiotamron was capable of inhibiting colonization through the activation of the Hypoxia Inducible Factor (HIF)-1α. This transcription factor is an essential regulator of mammalian innate defense, that, once activated, induces the production of the Cathelicidin-AMPs LL37, a critical immune effector for limiting C. albicans colonization. Conversely, the use of antifungal therapies can contribute to fungal dysbiosis in which some species are reduced while others expand. This was recently reported by Wheeler et al. who observed worsening colitis and allergic airway disease in experimental mice models. The administration of oral antifungal therapies correlated with an increase in Aspergillus sp., Wallemia sp. and Epicoccum sp. Colonization, whereas Candida sp. colonization was decreased.

Notwithstanding iatrogenic factors, many metabolic diseases, including GI disorders, have been linked to disturbances in C. albicans colonization. Over-colonization observed during bacterial dysbiosis may aggravate the severity of ulcers and inhibit healing associated with IBD. Additionally, a reduced diversity in both the fungal and bacterial gut flora, with a specific increase in the Candida genus, was reported in IBD patients. Recently, Sokol et al., highlighted a higher proportion of C. albicans in stools of IBD patients compared with healthy subjects, which points to a disease-specific fungal mycobiota dysbiosis. Collectively, these data strongly suggest the involvement of C. albicans in the pathogenesis of IBD.

It is now clear that overgrowth of C. albicans on GI mucosal surfaces contributes to disseminated candidiasis, especially in weakened patients in the hospital setting who are exposed to iatrogenic factors that favor C. albicans’ colonization, such as antimicrobial therapies and/or chemotherapies. However, when C. albicans colonization is associated with a metabolic disorder, including GI disorders, it is not clear whether the increased colonization results from or contributes to the pathogenesis of the disorder. Further studies are expected to specify (i) the inter-communication between C. albicans and bacteria at the species or community level in the gut, with emphasis to mixed biofilms and their role in the gut homeostasis and GI disorders; (ii) the influence of C. albicans’ over- or sub-colonization on the host metabolism and local or systemic immune response and (iii) the biological features of C. albicans associated with various digestive disorders.

**Interaction of C. albicans with the gut mucosal barrier**

**Tackling the AMPs armory and the mucus barrier**

As seen above, bacteria are essential for an efficient innate immune response against C. albicans, notably through the induction of AMP production, including LL37, histatin 5 and β-defensins. These AMPs exert anti-Candidal activities by (i) direct induction of cell death through mechanisms promoting pore formation, membrane depolarization and/or osmotic dysregulation in yeasts, (ii) immune modulation (through the promotion of PMNs/monocyte recruitment, TNF-α expression, chemoattraction of immature DCs and T cells) restraining C. albicans proliferation, and (iii) the repression of C. albicans virulence traits (e.g. α-defensin-6 prevents adherence to and invasion into enterocytes as well as biofilm formation) (Reviewed in Swidergall et al., 2014). During commensalism, the continuous but weak Pathogen Associated Molecular Patterns (PAMPs)/PRRs interactions lead to a low level of Nuclear Factor kappa B (NF-kB) pathway activation and so to a basal level of production of AMPs. Upon increased colonization and infection, a strong up-
C. albicans has developed a three-phase strategy to avoid the candidal activities of AMPs. First, C. albicans secretes peptide effectors which protect against a broad range of AMPs. This is exemplified by the Msb2 membrane glycoprotein whose extracellular domain, i.e. Msb2*, is released after cleavage in large amount in the extracellular environment, inactivating a large panel of AMPs. Interestingly, some data suggest the involvement of secreted aspartyl proteases (Saps) in the cleavage and release of Msb2*, while other observations corroborate the putative involvement of Saps as direct inhibitors of AMPs. The proteolytic activities of Saps (Sap1-4, Sap8 and Sap9) were reported to reduce the antifungal activity of the AMP LL-37. Second, in response to AMPs, C. albicans is able to express the drug efflux pump gene Flu1, allowing the AMPs to be outsourced from the intracellular compartments of the fungus. Third, the fungus is able to regulate signaling pathways, such as the HOG (High-osmolarity glycerol) pathway, which are key elements in survival to various AMPs. Knowing that the HOG pathway is involved in both the regulation of the ROS production and the production of ATP by the mitochondria, and that ROS production and ATP efflux is induced by various AMPs, this HOG pathway may exert a key function in the survival of C. albicans to AMPs by downregulating ROS production and ATP efflux.

It is assumed that the AMPs release in the intestinal environment, especially in the mucus layer, is conditioned by the composition of the gut microbiota that interacts with AMP-secreting cells (mainly PCs and PMNs). Consequently, dysbiotic states modify the panel and concentration of AMPs secreted in the gut lumen. However, less is known about the direct regulation of the secretion of AMPs by C. albicans and the gut microbiota. Interestingly, in this context, microarray-based transcriptomic analyses of intestinal epithelial cells interacting with C. albicans did not report overexpression of AMPs-related genes following infection, whereas a strong expression of AMPs (especially DEFB4) was observed in oral cells challenged with the fungus. Once more, these observations corroborate the view that molecular and cellular features characterizing C. albicans interactions depend on the type of host cell. However, no in-depth study has focused on the regulation of AMP secretion by C. albicans in gut-associated PCs and PMNs.

In addition to evading AMPs, C. albicans has to cross the mucus layer to access and adhere to the layer of IECs. The mucins that mostly make up this protective layer modulate the morphology and physiology of C. albicans, as exemplified by the mucin polymer Muc5AC expressed in the lung and the stomach that downregulate the expression of a range of genes related to adherence, filamentation and biofilm formation in C. albicans. Moreover, the mucin Muc7 has been reported to exert a direct antimicrobial effect upon C. albicans in the oral cavity. Nevertheless, the effect of mucins on colonization and dissemination of C. albicans in the gut remains to be specified.

C. albicans has however developed strategies to circumvent the mucus protective layer. C. albicans is able to adhere to mucins in a pH-independent process involving hydrophobic interactions that allow the non-specific binding of C. albicans to the 66-kDa cleavage product of the 118kDa C-terminal glycoprotein backbone of mucins. Whereas the involvement of specific C. albicans' ligands remains to be specified, Böhm et al. recently identified transcription regulators in C. albicans, including ZCF8, ZFU2 and TRY4, that favor (i) the yeast form of C. albicans more prone to colonize the gut in mice and (ii) adherence to mucins and mucus-producing IECs. After adhering to mucins, which is critical in initiating successful colonization to host mucosal surfaces, C. albicans degrades the GI mucus layer by secreting mucinolytic enzymes. Among them, Secreted Aspartyl Protease 2 protein (Sap2p) facilitates mucus penetration by promoting pore formation in the mucus layer using a strategy similar to that employed by enteropathogenic bacteria. Finally, C. albicans produces other Saps that degrade the sIgA scattered in the mucus layer, thus escaping the host innate immune response in part.
Interaction of *C. albicans* with enterocytes

In a susceptible host, once it has evaded the AMPs armory and the mucus layer, *C. albicans* adhere to IECs, cross the epithelial barrier and finally induce cellular damages leading to the loss of gut epithelium integrity.\textsuperscript{179}

*C. albicans* adherence to enterocytes. *Candida* sp. adherence to IEC is a key step in the physiopathological process that contributes both to the colonization and pathogenesis of disseminated candidiasis that mainly originate from the digestive mucosa.\textsuperscript{189} Heterogeneities have been reported in the adherence properties of different *Candida* species, *C. albicans* displays a greater capacity to adhere to epithelial cells *in vitro*, including to intestinal epithelial cells.\textsuperscript{190,191} Thus, *C. albicans* adherence to epithelial cells is a complex, dynamic and multifactorial process that requires a close relationship between the fungus and host proteins exposed at cell surfaces.\textsuperscript{192}

The capacity of *C. albicans* to adhere to host tissues depends on the type of epithelial cell. Indeed, *C. albicans* yeast forms display decreased adherence to differentiated enterocytes *in vitro* as compared with oral epithelial cells,\textsuperscript{10} suggesting that (i) oral cells may express specific molecules enhancing *C. albicans* attachment or (ii) the brush border lining the enterocyte’s layer displays unique features limiting the fungus’ ability to adhere. Following the first contact, most of the adherent yeast cells switch to the hyphal form,\textsuperscript{10} probably as a result of the physical contact with the epithelial surface.\textsuperscript{10,193} This is an important step since the expression of hyphal-associated genes will (i) strengthen adherence through enhanced expression of adhesins\textsuperscript{194,195} as well as (ii) favor the expression of hyphal invasins, enabling the fungus to enter the epithelial cells (see below). Another interesting observation from the early stages of interaction is the intimate entrapment of *C. albicans* hyphal tips within the microvilli that cover the surface of the enterocytes, a phenomenon that probably reinforces the attachment to the epithelial surface.\textsuperscript{10,196,197} Finally, hyphal forms of the fungus conglomerated to form aggregates that adhered to the surface of enterocytes, a phenomenon that was not observed with oral cells.\textsuperscript{10} It is possible that aggregation of *Candida* cells indirectly promote attachment of the fungus to the surface of enterocytes.\textsuperscript{198} Collectively, these observations strongly suggest that enterocytes express specific cues that influence the attachment of *C. albicans*. This view is supported by observations from Sohn et al. who investigated the transcriptional response of *C. albicans* adhering to different substrates, including vaginal and intestinal cells, and abiotic surfaces, for different periods of time.\textsuperscript{197} These authors reported subsets of genes that were specifically expressed in adherent conditions as compared to suspension cultures. Furthermore, the transcriptional response of the fungus differed significantly depending on the adhesive surface (including enterocytes). The response was globally close early on, but differences became more pronounced as the interaction progressed. These observations suggest the ability of *C. albicans* to sense and to adapt its transcriptional program to subtle variations in the adherent surface.\textsuperscript{197}

In addition to passive van der Waals forces and hydrophobic interactions that probably contribute to the initial contact of *C. albicans* on epithelial surfaces,\textsuperscript{199} expression of surface molecules (adhesins) is a key biological feature of the fungus, allowing its attachment to host tissues (both as a commensal or a pathogen),\textsuperscript{200} to abiotic surfaces, and to other microorganisms or *Candida* cells\textsuperscript{201} (reviewed in \textsuperscript{190,202,203}). The major *C. albicans* adhesins are GPI-anchored glycoproteins that are expressed by yeast or hyphal forms of the fungus or both, including the multifunctional agglutinin-like sequence (Alsp) proteins family, the hyphal wall proteins (Hwp) family, the IPF family, the F/Hphally upregulated protein or Ifi/Hyr protein family, and the Epithelial adhesin proteins (Eap) family.\textsuperscript{190,202} Furthermore, *C. albicans* expresses numerous other protein adhesins that have not yet been fully characterized in terms of structure and/or capacity to mediate adherence to epithelial cells such as fimbriae, Csh1, Ywp1, Pra1, proteins of the Sap family and others (Reviewed in \textsuperscript{190,202–204}). Though many of these adhesins have been reported to promote adherence of *C. albicans* to epithelial cells, few investigations have focused on enterocyte interaction. Sohn et al. observed an upregulation of *HWP1* in the early stages of the *C. albicans* and enterocyte interaction, suggesting
its involvement in the attachment of the fungus to the Caco-2 enterocytic cell line.\textsuperscript{197} Similarly, Hwp2p and Int1p have been reported to contribute to adherence of the fungus to the HT-29 human intestinal epithelial cell line \textit{in vitro}.\textsuperscript{396,205} Finally, a \textit{C. albicans} double mutant for the putative \(\beta\)-glucanase mannoprotein Mp65, defective in hypha and biofilm formation, displayed reduced adherence to plastic\textsuperscript{206} and epithelial cells including enterocytes.\textsuperscript{207,208} Given the role of Mp65 in cell wall organization and stability, it is plausible that deletion of the \(MP65\) gene affects the expression of other adhesins at the surface of \textit{C. albicans} cells, indirectly altering its adherence capabilities.\textsuperscript{207} However, observations that blocking antibodies specific for Mp65 strongly decrease adherence of wild-type \textit{C. albicans} to plastic\textsuperscript{206} and epithelial cells\textsuperscript{208} are in line with the direct contribution of Mp65 as an adhesin in \textit{C. albicans}.

In addition to the protein nature of adhesins and given the high content of the yeast cell wall in carbohydrate components, \textit{C. albicans} can also adhere to enterocytes through polysaccharidic molecules expressed at the cell wall surface.\textsuperscript{204,209} Indeed, Timpel \textit{et al.} reported first that a \textit{pmt1\alpha/\alpha} deletion mutant, a gene encoding a mannosyltransferase involved in the O-glycosylation pathway, displayed reduced adherence to enterocytic Caco-2 cells, suggesting a role for the O-linked carbohydrate content of the cell wall in the adherence of \textit{C. albicans} to enterocytes.\textsuperscript{210} Additional observations reported the contribution of the N-glycosidic part of the cell wall in the adherence of \textit{C. albicans} to enterocytes. Indeed, in competition experiments based on a panel of carbohydrates, Dalle \textit{et al.} observed a drastic dose-dependent reduction in the adherence of \textit{C. albicans} to enterocytic Caco-2 cells with synthetic \(\beta\)-1,2 oligomannosides and to a lesser extent with \(\alpha\)-1,2 oligomannosides, two glycans of the N-linked moiety of the cell wall.\textsuperscript{211} Unlike \(\alpha\)-1,2 oligomannosides, \(\beta\)-1,2 oligomannosides are rare structures in living systems, and their presence has been reported in only few bacterial and yeast species.\textsuperscript{212,213} However, they are prominently expressed in \textit{C. albicans}.\textsuperscript{214} They reside in the yeast wall associated with N-glycans of a high polymer of mannoses bound to a peptide, the phosphopeptidomannan (PPM) and mannoproteins (MPs) as well as to the glycan copula of a glycolipid of the family of mannose-inositol-phosphoceramides, \textit{i.e.} phospholipomannan (PLM).\textsuperscript{214,215} They contribute to the virulence of \textit{C. albicans} thanks to their immunomodulatory and adhesin properties.\textsuperscript{214}

Interestingly, the inhibitory effect obtained with the synthetic \(\beta\)-1,2 oligomannosides was higher than the other tested carbohydrates including the \(\alpha\)-1,2 oligomannosides.\textsuperscript{211} This strongly suggests that N-glycans specific to the \textit{C. albicans} cell wall contribute to their attachment to enterocytes. This confirms \textit{in vivo} observations that reported less \textit{C. albicans} gastrointestinal colonization in infant mice orally fed with synthetic \(\beta\)-1,2 oligomannosides, then in these orally fed with \(\alpha\)-1,2 oligomannosides.\textsuperscript{211,216}

Altogether, these data support the hypothesis that proteic and carbohydrate adhesins contribute to the attachment of \textit{C. albicans} to IECs, but further studies are required to better characterize the contribution of each of these adhesins. In addition, soluble factors from the extracellular matrix as well as serum proteins have been suggested as potential mediators of the indirect attachment of \textit{C. albicans} to mucosal surfaces.\textsuperscript{204,217} Similarly, specific ligands from host-cell surfaces, including proteins of the integrin and cadherin families, have reportedly facilitated the adherence of \textit{C. albicans} to epithelial cells.\textsuperscript{196,218}

However, the exact nature of the host factors that influence attachment remains to be specified.

\textbf{\textit{C. albicans} invasion into the enterocytes.} \textit{C. albicans} has developed several strategies to invade and further damage host epithelial cells. The yeast-to-hyphae transition in \textit{C. albicans} is pivotal for epithelial invasion, contributing to two different well-documented mechanisms of invasion: (i) epithelial-driven endocytosis of hyphal forms,\textsuperscript{10,220} and (ii) \textit{C. albicans}-driven active penetration.\textsuperscript{10,221–225} Endocytosis is considered an early event, seeing as it occurs within the first 4 hours of the interaction,\textsuperscript{224} whereas invasion at later stages seems mainly driven by active penetration.\textsuperscript{10,217,225} In fact, these two mechanistically distinct routes of invasion probably occur differentially depending on the epithelial cell type encountered by the fungus, as a result of the temporal and/or spatial availability of the epithelial receptors that are necessary for mediating induced endocytosis.\textsuperscript{219} For instance, when both mechanisms are present during a \textit{C. albicans} invasion of oral epithelial cells, active
penetration is the only process driving invasion of the enterocytes \textit{in vitro} at the early stages of the interaction.\textsuperscript{10} However, recent evidence suggest that endocytosis may occur later in time and that alternate routes may allow the translocation of \textit{C. albicans} through the gut barrier\textsuperscript{9} (Figure 4).

**Endocytosis of \textit{C. albicans}**. Endocytosis was first described for \textit{C. albicans} cells interacting with \textit{in vitro} models of endothelial or oral epithelial cells. The filamentous forms of the fungus were capable of triggering the formation of pseudopod-like structures at the surface of these host cells,\textsuperscript{193,194,220} leading to the partial engulfment of the hyphae and its progressive internalization into host cells.\textsuperscript{193,194,220} This host-cell mechanism is mainly driven through a Zipper-like actin filament-dependent process as demonstrated by the drastic decrease in the internalization of \textit{C. albicans} cells into oral and endothelial cells pretreated with the actin polymerization inhibitors Cytochalasin D and Lancuntrulin A.\textsuperscript{10,194,220} However, additional molecular processes contribute to endocytosis of the fungus, including macropinocytosis\textsuperscript{10} and the clathrin-dependent endocytic machinery.\textsuperscript{226} In addition, endocytosis is independent of the viability of the fungus since heat-killed hyphal forms of \textit{C. albicans} are endocytosed with the same efficiency as live hyphae.\textsuperscript{10,220} However, endocytosis of dead hyphae was not associated with cellular damage, suggesting that other(s) factor(s)

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Invasion of \textit{C. albicans} through the intestinal epithelial barrier.}
\end{figure}

Schematic representation of the different mechanisms used by \textit{C. albicans} to translocate through the gut mucosa: (i) the transcellular route, (ii) the paracellular route, (iii) the translocation through M cells, and (iv) the alternate route that may occur. \textit{Als3}, Agglutinin-Like Sequence 3; \textit{Ssa1}, Heat shock protein \textit{ssa1}; \textit{Hwp1}, Hyphal wall protein 1; \textit{Saps}, Secreted Aspartyl Proteases; \textit{CL}, \textit{Candida} lycsin; \textit{TJs}, Tight Junctions; \textit{LDH}, Lactate dehydrogenase; \textit{Ca2+}, Calcium.
produced by viable forms of the fungus may be necessary to cause cellular damage in both endothelial and oral epithelial cells.220,227

Two fungal invasins were reported as major stimulators of the endocytic machinery.194,228 First, the multifunctional hypha-specific surface protein Als3, a key virulence factor for C. albicans, acts as an invasin by triggering its own endocytosis by endothelial and oral human epithelial cells. N- or E-cadherin expressed at the surface of endothelial and oral epithelial cells, respectively, were identified as putative host cell receptors for this invasin.194,229 Finally, in silico analysis reported molecular similarities between Als3/E-cadherin and E-cadherin/E-cadherin interactions, suggesting the molecular mimicry of Als3 with cadherins.194 Interestingly in the context of C. albicans interaction with intestinal epithelial cells, Goyer et al. reported that Als3 participates in the E-cadherin-independent endocytosis of C. albicans into enterocytes displaying altered tight junctions (TJs) (see below for more details about the role of TJs during C. albicans invasion into enterocytes). Indeed, the specific blockade of E-cadherin by the SHE78-7 neutralizing antibody did not modify internalization of C. albicans into enterocytes displaying altered TJs.9 This corroborated other observations reporting a partial reduction in C. albicans endocytosis into oral epithelial cells when inhibiting E-cadherin function,230 suggesting that other(s) host-cell receptor(s) may contribute to the Als3-driven endocytosis of the fungus. A second invasin, Ssa1, expressed at the surface of C. albicans hyphae and belonging to the Hsp70 family of heat shock proteins, was found to contribute to cadherins-dependent endocytosis of the fungus into endothelial and oral epithelial cells.-228 Indeed, C. albicans ssa1Δ/Δ exhibited reduced endocytosis into endothelial and oral epithelial cells, that was associated with less cellular damage, a decrease in adherence to endothelial and oral epithelial cells and attenuated virulence in a mouse model of oropharyngeal candidiasis.228 Surprisingly, the C. albicans double mutant ssa1Δ/Δals3Δ/Δ displayed reduced endocytosis, similar to the single mutant als3Δ/Δ, suggesting (i) the possible binding of Als3 and Ssa1 to the same host receptor and/or (ii) a cooperative function of both Als3 and Ssa1 acting as a multiprotein complex.228 Finally, other invasins probably contribute directly or indirectly to the endocytosis of C. albicans,217,230 as highlighted by Wächtler et al., who observed reduced endocytosis of killed hyphae of the C. albicans sap1-3Δ/Δ and sap4-6Δ/Δ deletion mutants into oral cells.217 However, the exact nature of the Saps as well as their direct or indirect involvement in the endocytic mechanism is not yet clear.

Collectively, these observations strongly suggest that endocytosis of C. albicans into epithelial cells is a complex mechanism that involves C. albicans hyphal-invasins including Als3, Ssa1 but possibly other invasins that remain to be specified. The interaction of such invasins with host-receptors, including cadherins but also probably other receptors, is necessary for triggering this process.217 Zhu et al. highlighted that the involvement of Epithelial Growth Factor Receptor (EGFR) and HER2 as cadherin-independent host receptors during the endocytosis of C. albicans into oral epithelial cells.230 However, the exact nature and function of such invasins and host receptors in the endocytosis of C. albicans into enterocytes displaying altered TJs remains to be specified.

Active penetration. Active penetration is a fungal-driven process and requires viable forms of the fungus. Similar to endocytosis, active penetration exploits the yeast-to-hyphae transition of C. albicans, which germinate and produce hyphae that progressively elongate and penetrate the epithelial cells.10,219 This invasion mechanism is of prime interest since it is the only one that allows C. albicans to gain entry to enterocytes with intact intercellular junctions in vitro.9–11 Scanning Electron Microscopy (SEM) observations of Candida-infected enterocytes did not reveal pseudopod-like structures surrounding C. albicans hyphae, which is a typical feature of endocytosis. By contrast, a depression in the cell surface was observed around the C. albicans entry site, probably as the result of an active process of the extending hyphae forcing entry either directly into the apical surface or at intercellular junctions between adjacent enterocytes. These observations were supported by the fact that pretreatment with endocytosis inhibitors does not inhibit the uptake of the fungus into enterocytic Caco-2 cells.10 The contribution of fungal hydrolases to this process has been investigated but remains
Notably in the gut barrier, Saps contribute to the active penetration of *C. albicans*. The *C. albicans* deletion mutants *sap1-3Δ/Δ* or *sap4-6Δ/Δ* displayed moderate but significant reduction in their ability to invade enterocytes. In addition, treating the fungus with the aspartic protease inhibitor pepstatin A reduced enterocyte invasion in a dose-dependent manner. The role of other hydrolases, including lipases and phospholipases B1, did not obviously contribute to active penetration of *C. albicans* into enterocytes. Altogether these results suggest that active penetration of *C. albicans* into intestinal cells is likely to occur through molecular mechanisms combining the mechanical pressure exerted by elongating hyphae and the lytic activities of Saps.

Interestingly, Als3, a major invasin that contributes to induced endocytosis, reportedly facilitates the active penetration of *C. albicans* into oral epithelial cells, but probably through an indirect mechanism that favors the binding of the two structures. Als3 also seems to play a role in invasion since a *C. albicans* deletion mutant *als3Δ/Δ*, which is not defective in hyphal formation, was less able to invade intact enterocytes, which are not able to internalize the fungus through endocytosis.

Interestingly, in an attempt to decipher the molecular basis of the interaction of *C. albicans* to epithelial cells, Wächtler et al. investigated the abilities to adhere to, invade and cause damage to oral and intestinal epithelial cells, of a set of 26 mutants deleted for genes predicted to be and/or previously reported as major contributors to host-*C. albicans* interaction. Whereas *EFG1* and its upstream regulators appeared essential for all stages of the infection process, other genes displayed discrete but significant functions in specific stages of the interaction. Nine genes were identified as “damage-associated” since the corresponding deletion mutants were still able to invade oral epithelial cells but without damaging them. Surprisingly, six of these mutants (i.e. *gpd2Δ, gpp1Δ, cka2Δ, bcr1Δ/Δ, hwp1Δ, bud2Δ* and *rsr1Δ*) displayed a strong and significant decrease in invasion into enterocytes. This suggests that the genes involved in glycerol accumulation (*GPP1* and *GPD2*) and directed hyphal growth (*BUD2* and *RSR1*) are necessary for the active penetration of *C. albicans* into enterocytes but not into oral cells.

Together, these observations strongly support the view that *C. albicans* requires some specific genes to invade enterocytes but not oral epithelial cells, reflecting the ability to adapt to specific cell environments by expressing biological factors that can contribute differentially to specific stages of the infection process.

**The paracellular route.** Several studies have suggested a paracellular route involving the proteolytic cleavage of the intercellular adherens junction (AJ) protein E-cadherin in both oral epithelial cells and IECs. AJS are located immediately below the TJs, and are mainly composed of proteins of the cadherin family including E-cadherin. AJs together with TJs form a junction belt that ensures the architectural cohesion of the intestinal epithelium.

While active penetration has been described as the predominant mechanism of *Candida* invasion into IECs, in 2016 Goyer et al. observed that endocytosis of *C. albicans* can also occur during interaction with IECs *in vitro*. They demonstrated that TJs play a protective role in the early steps of the interaction by limiting endocytosis-mediated *C. albicans* invasion into enterocytes. While intact IECs are mainly invaded through active penetration, pharmacologically altered TJs are invaded by active penetration and induced endocytosis, through molecular mechanisms involving, at least in part, the hyphal-associated invasin Als3. So, in addition to demonstrating the role of TJs in limiting the invasion of IECs by *C. albicans*, this study highlights the putative harmful effects of extrinsic factors that alter the integrity of TJs, thereby allowing *C. albicans* to invade through the gut barrier. This corroborates reports of clinical situations where therapies or medical practices may alter the permeability of the digestive tract, consequently promoting the translocation and hematogenous dissemination of common residents of the gut microbiota, including *C. albicans*. Interestingly, recent findings indicate that *C. albicans* itself can alter the integrity of TJs. Using an *in vitro* model of the intestinal barrier, Böhinger et al. observed a barrier breakdown after 8 h of infection, as illustrated by the drastic decrease in the Trans-Epithelial Electrical Resistance (TEER)
of C2BBe1 (a clone of Caco-2 cells) intestinal epithelial cells interacting with \textit{C. albicans}. This breakdown was not related to cell death since C2BBe1 cells were not damaged at this point in time. In addition, the drop in TEER required the fungal yeast-to-hyphae transition since the \textit{efg1Δ/efg1Δ} deletion mutant, unable to produce hyphae, did not induce barrier breakdown or cell death. Along with barrier breakdown, a strong decrease in the level of TJ proteins, including occludin, JAM-A, Claudin –1, –3 and –4, was observed by Western-blotting on whole infected-cell extracts, suggesting that the barrier breakdown results from the loss of these proteins. This was confirmed by immunofluorescence testing which found a progressive extinction of Occludin, Claudin-1 and 4 and JAM-A staining after 10 h of infection. All in all, this study showed that a barrier breakdown occurs during infection by \textit{C. albicans} and this is related to a decrease in TJ protein levels and their concomitant disappearance from cell-cell borders.\cite{177} Recently, Allert et \textit{al.} observed the ability of the \textit{ece1Δ/Δ} mutant to compromise epithelium integrity and to translocate across the intestinal epithelial barrier through damage-independent factors and without damaging the cells.\cite{179} The authors hypothesized that these factors probably alter the cell-cell connections (i.e. TJs or adherens junctions), facilitating paracellular translocation. Focusing on the effect of Saps on the promotion of the degradation of the E-cadherin protein during \textit{C. albicans} infection, they studied mutants lacking various SAP genes (i.e. \textit{sap1-3Δ/Δ}, \textit{sap5Δ/Δ}, \textit{sap4-6Δ/Δ} and \textit{sap9/10Δ/Δ}). Unfortunately, no translocation defect was observed with the mutants. However, the reduced ability of the \textit{sap1-3Δ/Δ} mutant to translocate through the blank transwell insert without cells cannot rule out the possible minor role of SAPs in the paracellular route of translocation.\cite{179}

Collectively, these are important observations that point to the paracellular route as a possible mechanism used by \textit{C. albicans} to translocate through the intestinal barrier. This mechanism may favor the passage of \textit{C. albicans} cells between enterocytes without invading or damaging intestinal cells.\cite{10, 193} However, it is clear now that easier access to the basolateral site of intestinal cells promotes fungal invasion through both active penetration and induced endocytosis.\cite{9} Finally, \textit{C. albicans} itself is capable of altering the integrity of TJs, secondarily promoting its own translocation.\cite{177} However, the extent to which the paracellular route promotes intercellular transmigration of \textit{C. albicans} (associated or not to epithelial invasion and damage) remains to be specified.

\textbf{\textit{C. albicans}-induced epithelial cell death and mucosal damage.} Late stages of the infection of intestinal cells are characterized by a loss of barrier integrity associated with the destruction of IECs invaded by \textit{C. albicans} (Figure 4).\cite{203} It is possible that the barrier breakdown observed in the late stages, as a consequence of alterations in intercellular junctions,\cite{177, 233} triggers host-cell signaling pathways that promote inflammation, the activation of inflammasomes and apoptotic events, ultimately leading to necrosis of the enterocytes.\cite{43} Invasion by \textit{C. albicans} also actively contributes to enterocyte damage and cell death.\cite{203} Until recently, it was generally believed that \textit{Candida} invasion resulted in the death of infected epithelial cells possibly through mechanisms involving necrosis and/or apoptosis.\cite{231} However, the invasion of epithelial cells \textit{per se} is not always clearly associated with cell damage.\cite{179} In fact, initial invasion of oral, vaginal or intestinal epithelial layers causes little measurable cell death.\cite{10, 193} Conversely, the later phases of \textit{C. albicans} invasion into IECs are associated with epithelium damage mainly due to the mechanical elongation of the hyphae.\cite{219} However, the identification of a specific virulence factor inducing cell damage has remained elusive.

A cytolysin produced by \textit{C. albicans}, named \textit{Candidalysin} (CL), was recently identified; it is thought to be the missing link between hyphae formation and damage to host cells.\cite{179, 238} \textit{CL} is a 31-amino-acid peptide generated from the pre-protein \textit{Ece1} (Extent of cell elongation 1) (271 amino acids), which is encoded by the \textit{ECE1} gene belonging to the eight core filamentation genes of \textit{C. albicans} and highly expressed during hyphae formation.\cite{239} Previous studies had shown that the seven lysine-arginine dibasic amino acid motifs present in the \textit{Ece1} pre-protein can be recognized and cleaved by a subtilisin-like serine protease, Kex2, in the yeast Golgi apparatus.\cite{240}
CL is one of the cleaved peptides generated from Ece1, and its α-helical structure allows it to intercalate and permeabilize the host cell membranes and subsequent cell lysis when secreted in sufficient amount. In oral epithelial cells, CL triggers a danger-response signalling pathway and activates epithelial immunity. Moreover, the permeability of the cell membrane is enhanced by a positive charge at the carboxy terminus of the peptide which triggers an inward current concomitant with calcium influx. Recent observations have confirmed the importance of CL during the translocation of *C. albicans* through the intestinal barrier in vitro. Allert et al. screened more than 2000 *C. albicans* gene deletion mutants to identify fungal factors involved in *C. albicans* gut translocation, leading to the identification of several genes associated with cellular damage including PRN4, orf19.2797, NRP2, AAF1, HMA1, TEA1, orf19.3335, PEP12 and ECE1. Focusing on these nine corresponding mutants, eight of them, including ece1Δ/Δ, showed a significant decrease in their ability to induce damage at 24 h post-infection. Given the critical role of CL for oral and vaginal epithelial cell damage, the authors investigated the role of CL during *C. albicans* gut translocation using a *C. albicans* mutant that lacked only the CL-encoding region within ECE1 (ece1 Δ/Δ + ECE1Δ184–279 mutant). They observed that both ece1 Δ/Δ and ece1 Δ/Δ + ECE1Δ184–279 mutants were unable to induce damage and that their ability to induce damage was partially restored with the administration of synthetic CL. This demonstrated that a combination of both (i) hyphae formation and (ii) CL secretion were required for optimal damage induction. Necrotic cell death seems to be the major mechanism involved in damage observed during *C. albicans* translocation through enterocytes. Indeed, 24 h post-infection, no induced apoptosis (i.e. Annexin V staining) was observed while 40% of IECs were necrotic. In addition, damage was associated with a loss of epithelial integrity during the translocation of *C. albicans* through the intestinal epithelial layer. These studies highlight the key role of CL in *Candida* pathogenesis and provide a molecular explanation for the destructive activity of hyphae on the mucosal surface.

### Interaction of *C. albicans* with M cells

As mentioned above, several bacterial pathogens exploit M cells to invade mucosal tissues and cross the digestive epithelial barrier to reach the bloodstream. This suggests that entry through M cells is an essential step in the pathophysiology of many infectious diseases. In a recent in vitro study, Albac et al. demonstrated that *C. albicans* co-localizes with and preferentially invades M cells in a model of the enterocytic Caco-2 cells co-cultured with M-like cells, providing novel evidence that the fungus can use M cells as a portal of entry through the intestinal barrier. In addition to active penetration, F-actin-dependent endocytosis contributed to internalization of the fungus into M cells through a mechanism involving hypha-associated invasins such as Ssa1 and Als3. Moreover, fungal β-glucans can be endocytosed by M cells which, by virtue of their APC function, expose β-glucans to macrophages and dendritic cells associated with Peyer’s patches, thereby modulating the systemic immune response to *C. albicans*. Altogether these recent findings strongly support the view that understanding the contribution of M cells in sensing *C. albicans* as a commensal or a pathogen should provide new insights to the commensal role of *C. albicans* as well as to the pathophysiology and initiation of life-threatening systemic candidiasis. The exact molecular mechanisms by which *C. albicans* targets and translocates through M cells as well as the relevance of these interactions in vivo remain to be elucidated.

### Models to study interaction of *C. albicans* with the intestinal mucosa

For now, several models have been already used to study the interaction between *C. albicans* and the epithelial intestinal barrier. Surprisingly, when the gut barrier forms a complex environment involving several cell types, each with specialized functions, the in vitro models already described are mostly based on the use of only one cell type: enterocytes. Only one model investigated the interaction of *C. albicans* with two co-cultured cell types: enterocytes and M-like cells. However, new models are aimed at specifying the interaction of the fungus with AMPs, mucus and immune response.
cells in the gut environment, as well as with other specialized cells including PCs, and Goblets cells. All of the existing models (i.e. in vivo and in vitro) are summarized in Table 1 and Table 2.

**Conclusions**

Formerly described as a commensal that exists on the mucosal surfaces of most healthy individuals, *Candida albicans* is an opportunistic pathogen that causes infections ranging from superficial to life-threatening disseminated infections, especially in the ever-growing population of vulnerable patients in hospital settings. In these situations, the fungus takes advantage of its host thanks to disturbances in the host-defense system and the mucosal microbiota. Overwhelming evidence suggests that the gastrointestinal tract is the main source of disseminated *C. albicans* infections. Some of the major risk factors for disseminated candidiasis include damage to the mucosal intestinal barrier, immune dysfunction, and antibiotic-induced dysbiosis of the resident microbiota.

| Table 1. *In vitro* models developed to study the interactions between *Candida albicans* and the epithelial intestinal barrier. |
| --- |
| **Cell lines** | **Experimental procedures** | **Features** | **References** |
| Colon adenocarcinoma derived cell line Caco-2 (ATCC® HTB-37™) | Routinely cultured in DMEM medium supplemented with 10% FBS, pyruvic acid, L-glutamine and nonessential amino acids without antibiotics or antifungal agents in a humidified incubator at 37°C in 5% CO₂ | Monolayers displayed several morphological and functional characteristics of mature enterocytes | 10, 233 |
| C2BBel | Routinely cultured in DMEM/Ham’s F12 medium supplemented with 0.1 Vol. FBS, glucose, stable glutamine and proxymetin in a humidified incubator at 37°C in 10% CO₂ | Polarized monolayers (Caco-2 subclone) | 177 |
| Human enterocytes Caco-2/Isolated murine B Lymphocytes from Peyer’s patches | Caco-2 culture in insert for 14 days then co-culture with isolated murine B Lymphocyte from Peyer’s patches. M cell differentiation obtained 6 days post LB initiation. | Heterologous co-culture | 241 |
| Human enterocytes Caco-2/LB Raji | Caco-2 culture in insert for 10 days then co-culture with LB Raji. M cell differentiation obtained 6 days post LB initiation. | Homologous co-culture | 11, 243 |

| Table 2. *In vivo* models described to study the interaction between *Candida albicans* and the epithelial intestinal barrier Murine models of intravenous disseminated candidiasis. |
| --- |
| **Mice strains (sex)** | **Experimental procedures** | **Features** | **References** |
| DBA/2N (M or F) | - Immunocompetent or immunocompromised mice | Well characterized Reproducible Rapid spread | 244–247 |
| CFW (M) | - Infected intravenously with *C. albicans* via the tail vein | | |
| CD-1 (F) | | | |
| CBA/H (us) | | | |
| BALB/c (M or F) | | | |
| C3H/HeJ (M) | - Diet supplemented with yeasts administrated (i) in food or (ii) in drinking water or (iii) by gavage | Mimic the yeast physiopathology in Human | 14, 245, 248–253 |
| BALB/c (M or F) | - Gut colonization argued by stool culture | Blood dissemination delayed 14 to 21 days after the induction of the barrier rupture | |
| CD-1 (F) | - Gut mucosa breakdown induced by (i) hypo-protein diet or (ii) administration of DSS or (iii) administration of immunosuppressive treatments (Cyclophosphamide, succinate methylprednisolone sodium, cyclosporine, 5-Fluorouracil) | | |
| CBA/H (us) | | | |
Clearly, translocation of \textit{C. albicans} through the intestinal barrier into the bloodstream is a critical step in the initiation of invasive candidiasis, which makes it important to understand the mechanisms by which \textit{C. albicans} interacts with the gut barrier. Given the specific cues shared by intestinal cells and the specific environment of the gut lumen, the bulk of knowledge acquired when studying interaction of \textit{C. albicans} with other mucosa, including the oral mucosa, is not fully transferable to the behavior of the fungus in the gut context.

A more precise view has emerged recently on how \textit{C. albicans} translocates through the gut epithelial layer. However, the nature of the fungal and host factors contributing to the translocation remain to be specified. In addition, many questions are still unsolved and remain to be explored. For instance, a lack of knowledge exists with regard to the specific molecular mechanisms allowing IECs to prevent fungal invasion and how \textit{C. albicans} can hijack them. The mechanisms by which \textit{C. albicans} interacts with specialized IECs such as PCs and goblet cells and their effects on gut homeostasis and/or the pathogenesis of candidiasis is still unknown. Similarly, the extent to which the maintenance of inter-cellular junctions is crucial to restraining \textit{C. albicans} invasion and how the fungus alters these junctions is still ongoing. In addition, little is known about how the biochemical components of the gut environment modulate the fungal factors and how \textit{C. albicans} resists these biochemical factors. Finally, from an immune point of view, the specific mechanisms and pathways involved during host response associated to commensalism or pathogenicity of \textit{C. albicans} need to be precise in the gut reservoir. For instance, though the contribution of the M cells in the translocation of \textit{C. albicans} is now obvious, the consequence of this mechanism on the priming of tolerant or protective immune response is still unknown. A better overall understanding of the interaction between \textit{C. albicans} and the intestinal epithelial barrier will help with the development of future therapies to avoid systemic candidiasis.

Importantly, with the advance of molecular tools to study microbiota components, new insights have emerged with regard to the association of GM dysbiosis with gastrointestinal or extra-gastrointestinal disorders where \textit{C. albicans} colonization is disturbed. When highlighting the intricacy of bacterial-fungal relationships in the GM, the consequences of these complex interactions upon the host and \textit{C. albicans} virulence needs to be clarified. Such information will help with the creation of new strategies to combat candidiasis, taking advantage of the existing interactions between bacteria and fungi in the gut microbiota. Co-infection models that closely mimic the interactions of the digestive microbiota and IECs are needed if we are to fully understand the pathophysiological mechanisms of candidiasis.

\section*{Abbreviation}

\begin{tabular}{ll}
Adenosin Triphosphate & ATP \\
Adherens Junctions & AJs \\
Agglutinin-Like Sequence & ALS \\
Anti-Microbial Proteins & AMPs \\
B Lymphocytes & LB \\
Candidalysin & CL \\
c-Jun N-terminal Kinase & JNK \\
Dendritic Cells & DCs \\
Epithelial Adhesin Protein & EAP \\
Epithelial Growth Factor Receptor & EGFR \\
E-twenty-six-specific sequence & Ets \\
Extent of cell elongation 1 & Ece1 \\
Extracellular-signal-Regulated Kinase & ERK \\
Follicle-Associated Epithelium & FAE \\
GastroIntestinal & GI \\
Gastrointestinally-IndUced Transition & GUT \\
Glyco-Protein 2 & GP2 \\
Gut-Associated Lymphoid Tissue & GALT \\
Gut-associated Microbiota & GM \\
Heat Shock Protein & HSP \\
High-osmolarity glycerol & HOG \\
Hyphal wall protein & Hwp \\
Hypoxia Inducible Factor & HIF \\
Inflammatory Bowel Disease & IBD \\
Intestinal Epithelial Cells & IECs \\
Intestinal Epithelium & IE \\
Isolated Lymphoid Follicles & ILF \\
Macrophages & Mφ \\
Mannoproteins & MPs \\
Mesenteric Lymph Nodes & MLNs \\
Microfold cells & M cells \\
Mitogen-Activated Protein Kinases & MAPK \\
Mucosal Immune System & MIS \\
Neutrophil cells & PMNs \\
Next Generation Sequencing & NGS \\
Nuclear Factor kappa B & NFκB \\
Paneth Cells & PCs \\
\end{tabular}
Disclosure of interest
The authors report no conflict of interest

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