Volume 8:1-10

UJEMI+

The Undergraduate Journal of Experimental Microbiology & Immunology (+Peer Reviewed)

The colonization of *Candida albicans* in the gastrointestinal tract and the subsequent human host response

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SUMMARY *Candida albicans* is a fungus that is part of the default microbiota of approximately 70% of the human population. It mainly inhabits the gastrointestinal (GI) tract and vagina. In most cases, this fungus does not cause harm in immunocompetent individuals. However, during immunosuppression or a general disruption of the bacterial microbiota, *C. albicans* can potentially become pathogenic by transitioning from a single-celled yeast to filamentous hyphae. The ability to transition between yeast and hyphal forms is a virulence property of *C. albicans*. This ability is thought to be a critical step in tissue invasion processes. While the science community has studied the path of *C. albicans* infections, the involved mechanisms, and the basic host response, there is a need for more studies into understanding the more minute details of the involved molecular changes in the gut epithelium, mucosal mast cells, and the specific responses the infections cause. This paper describes the mechanisms behind *C. albicans* infections in a human host and highlights the implications of these fungal interactions with the epithelial barrier and morphological transitions.

INTRODUCTION

While rare exceptions have been identified, *Candida albicans* is non-pathogenic in most healthy individuals; regardless, it is the most common human fungal pathogen implicated in intestinal diseases in individuals who are immunocompromised. For the immunocompromised population, *C. albicans* causes a myriad of mucosal and chronic infections annually (1, 5). It is also the causative agent of severe fungal infections, termed candidiasis. Candidiasis refers to cutaneous and mucosal infections and internal organ infections in these immunocompromised individuals.

C. albicans also has a myriad of virulence factors that explain its ability to invade hosts with both intact and compromised immune systems and cause infections (2). These factors include yeast-to-hyphal transitions, adhesions, biofilm formation, hydrolytic enzymes, thigmotropism, and toxins. As mentioned, yeast-to-hyphal transitions, known as morphogenesis, are a critical step in invading tissues as these transitions promote the breaching of mucosal surfaces. This dual nature is also needed for the fungus to survive in the host body; research has shown that Sir2, a protein, facilitates these transitions (2); however, it is important to note that in addition to Sir2, environmental conditions determine whether this transition takes place as well. Experiments revealed that *C. albicans* without the Sir2 gene did not form both true hyphae and pseudo-hyphae transitions while with sufficient nutrients, the same Sir2-mutant fungus formed more pseudo-hyphae but less true hyphae transitions.

Adhesions refer to biomolecules that ensure that the *C. albicans* adhere to host cells, which contribute to host recognition (2). Biofilm formation refers to dense groups of cells that adhere to both biotic and abiotic surfaces, and these dense communications of cells are

Published Online: September 2022

Citation: Ahmad Q. 2022. The colonization of *Candida albicans* in the gastrointestinal tract and the subsequent human host response. UJEMI+ 8:1-10.

Editor: Evelyn Sun, University of British Columbia

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highly resistant to the host immune system. The first step is for yeast cells to adhere to a certain surface to form a basal layer (2). Afterwards, biofilm development involves the growth of hyphal cells. As can be inferred, many of the proteins needed for hyphal formation proliferation are needed for biofilm regulation as both processes contribute to the maintenance of each other and perpetuate invasions of tissues. Hydrolytic enzymes refer to enzymes that promote infections, such as aspartic proteases and phospholipases (2). Aspartic proteases are secreted to damage tight junctions (TJs) to allow *C. albicans* to invade the intestinal barrier, and phospholipases' high extracellular activity has been credibly linked to increased pathogenicity (2). Thigmotropism, also known as contact sensing, is the ability to sense and react to certain changes in the surroundings; it also contributes to hyphal formation as morphogenesis is sensitive to alterations in surface contours and structures (3). Cytolytic fungal peptide toxins, such as candidalysin, are also secreted to damage to the epithelial barrier, which hinders the host immune response (3).

Typically, *C. albicans* is ubiquitous in nature and can balance its non-pathogenic potential with its pathogenic potential by reacting to the environment in which it exists (1). In immunocompetent individuals, the colonization of *C. albicans* outside the outer mucosal barrier of the GI tract does not lead to an infectious disease in most cases. In rare cases, *C. albicans* can infect immunocompetent individuals if outliner conditions, such as these individuals being in intensive care, having pre-existing conditions, or co-morbidities, are present (4). High levels of *C. albicans* colonization can be dangerous to hosts as this leads to *C. albicans* breaching the mucosal epithelial barrier, enhancing intestinal permeability, and activating the underlying cells of the immune system. Several circumstances favor higher colonization levels of *C. albicans*, such as intestinal inflammation perturbing the resident microbial community (1).

Studies have shown that there is a correlation between GI tract-related diseases and the high levels of *Candida* colonization. They have also proven that the immune system is unable to heal inflammatory lesions due to *Candida* colonization, which leads to this inflammation promoting even higher levels of *Candida* colonization (1, 5). This example illustrates how infections, such as candidiasis, are perpetuated; they are perpetuated because even instances of low-level inflammations in the GI lead to an increase in *Candida* colonization, which, in turn, promotes high levels of inflammation. This results in an activated immune response and gut immunopathology (1, 5). This paper reviews the homeostatic state of *C. albicans*, the role of the mucosal epithelial barrier during infection, and subsequently, the interaction between *C. albicans* and host immune cells, such as mast cells (MC), that aim to reduce *C. albicans* levels.

THE EPITHELIAL BARRIER

The intestinal tract is formed by epithelial cells that act as a dynamic barrier to pathogens and dietary antigens while exclusively absorbing nutrients (5, 6). Precise regulation of the epithelial barrier function is required for maintaining mucosal homeostasis and depends on barrier-forming elements within the epithelium. These elements include a series of intercellular junctions that consist of apical TJs, subjacent adherens junctions, and desmosomes (Fig. 1).

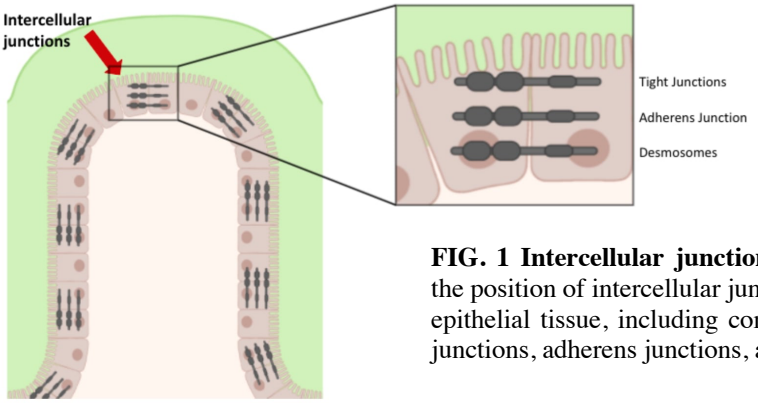

FIG. 1 Intercellular junctions. This visual depicts the position of intercellular junctions in relation to the epithelial tissue, including components such as tight junctions, adherens junctions, and desmosomes.

TJs are intercellular junctions that contribute to cell polarity and function to control the movement of solutes between intestinal epithelial cells (IECs). They function to protect IECs from *C. albicans* infections, and the protective features of these junctions are strengthened by probiotics (7). This defense mechanism can be circumvented by altering these TJs with enteric pathogens, which leads to the internalization of the hyphal form of this fungus due to endocytosis (7). The TJ backbone is composed of three main families of transmembrane proteins: claudins, occludins, and the Junctional Adhesion Molecule (JAM) protein family (5, 8). One of the proteins of the JAM family, JAM-A, is expressed in IECs and has been implicated in several aspects of regulating epithelial barrier function (5, 8). The epithelial barrier consists of structural components that aid in maintaining epithelial barrier integrity while TJs instead play a role in epithelial permeability (5). The JAM family of proteins, specifically JAM-A, has the most important role in the regulation of intestinal epithelial barrier function and mucosal homeostasis because it is a protein signaling molecule that regulates gastrointestinal permeability (5). JAM-A accumulates at TJs and is particularly abundant in IECs; IECs work to balance the gut microbial community and immune system (5, 8). An *in vivo* study showed that JAM-A-deficiency resulted in enhanced gastrointestinal permeability, suggesting that JAM-A plays a role in regulating the epithelial barrier and, thus, intestinal permeability (6). Other studies confirm that JAM-A-deficient mice are susceptible to inflammatory bowel disease (IBD), ulcerative colitis (UC), and a leaky gut epithelium (6). More recent studies have concluded that JAM-A plays a crucial role in maintaining epithelial barrier integrity, highlighting the importance of further research on the role of JAM-A in enhancing intestinal permeability during *C. albicans* infection (8).

The intestinal epithelium maintains mucosal homeostasis and balances pro- and anti-inflammatory factors. Dysregulation of these interactions results in the permeation of luminal antigens, immune responses, and epithelial barrier compromise; this can perpetuate pathologic mucosal inflammation and gut immunopathology. High-levels of *C. albicans* colonization results in the breaching of the epithelial barrier and subsequent activation of mast cells (Fig. 2) (1, 5). The physiological changes within the intestinal epithelium accompanying *C. albicans* infections have not been studied yet. Because *C. albicans* has been shown to breach the mucosal barrier in the gut, it is crucial to understand the molecular changes in the epithelium that accompany *C. albicans* infections.

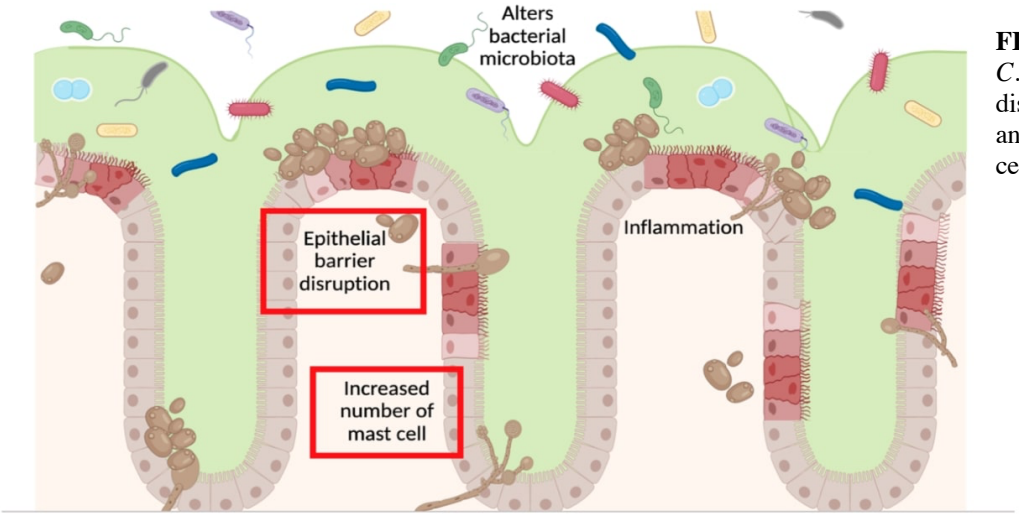

FIG. 2 Epithelial disruption. *C. albicans* overgrowth disrupts the epithelial barrier and results in increased mast cell production.

BALANCING THE HOMEOSTATIC STATE

Regulation of the epithelial barrier depends on balancing host and microbial factors in the mucosa. The intestinal epithelium consists of surface mucus layers, luminal commensal bacteria, and underlying immune cells that engage in complex interactions that maintain mucosal homeostasis. Colonization levels of *C. albicans* reveal a correlation between the fungus, host immunity, and the microbiome. Figure 3 portrays the homeostatic states of all the components involved in a *C. albicans* infection before a reaction takes place. The

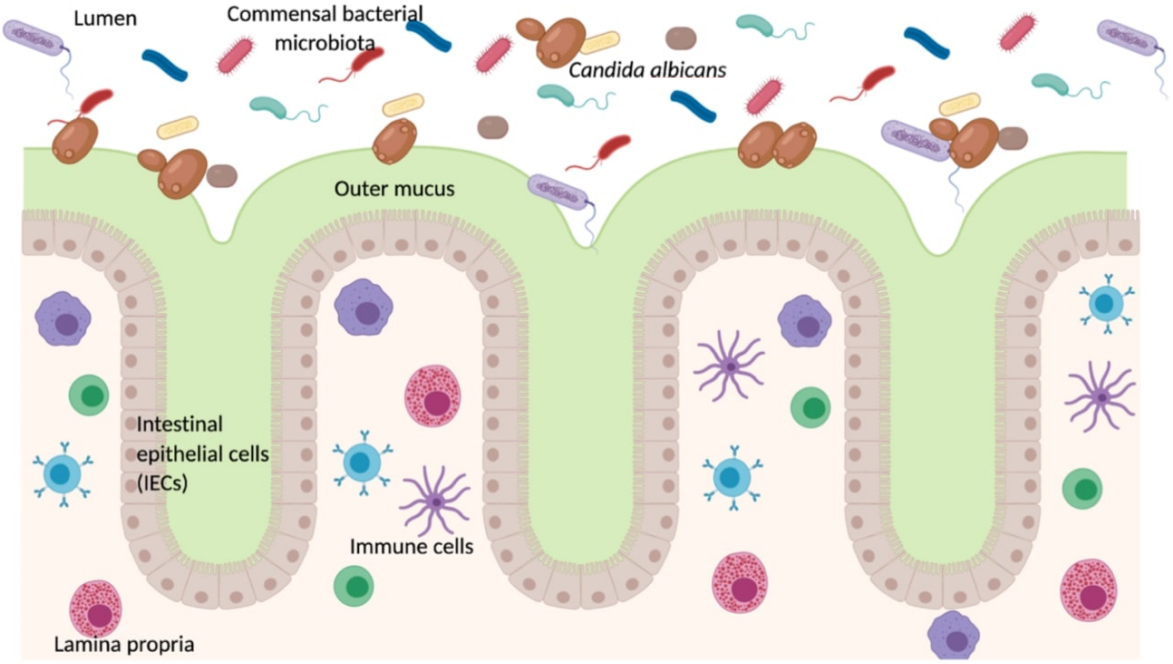

FIG. 3 Homeostatic statuses of *C. albicans*, the epithelial barrier, and mast cells. *C. albicans* is able to exist within the gastrointestinal microbiome at low fungal levels without invasion of the outer mucus layer and epithelial tissues. In turn, resident immune cells, including mast cells, remain quiescent and are not activated.

commensal bacterial microbiota and the populations of IECs and immune cells need to be maintained at pre-colonization levels (9, 10).

Any factor disrupting these balanced interactions leads to a compromised epithelial barrier, permeability to luminal antigens, and immune responses that can perpetuate pathogenesis. For example, an increment in *C. albicans* colonization occurs when the host experiences intestinal inflammation or antibiotic pressures (10). The inflammation or antibiotics disturb the normal levels of the microbiome community and host immunity, leading to the immune response of the GI tract. While *C. albicans* is exploiting the weakened immune system and abnormal microbial levels, it also simultaneously enhances its ability to transition from single-celled yeast to filamentous hyphae (10). As a result, hyphae fungi can breach the mucosal epithelial barrier, enhance intestinal permeability, and activate underlying cells of the immune system (9, 10).

BREACH OF MUCOSAL EPITHELIAL TISSUES

Impairment of intestinal barrier function has been widely implicated as a critical determinant in predisposition to GI diseases. Numerous groups, such as Yamaguchi et al. and Chen et al., have studied epithelial barrier function and enhanced gastrointestinal permeability in the context of GI inflammatory disease, food allergy, and *C. albicans* colonization (11, 13). Mucosal inflammatory diseases, such as IBD and its subsidiaries, are associated with impaired epithelial barrier function, often termed “leaky gut” (11). Enhanced intestinal permeability has also been linked to diabetes and allergic diseases, correlating with the severity of their clinical symptoms (12). Recent studies have suggested that *C. albicans* infections predict an effect on epithelial barrier function and intestinal permeability and can facilitate the permeation of food antigens (13). This suggests that GI *C. albicans* colonization impairs the GI mucosal barrier. Because the gut is the largest reservoir of *C. albicans*, it is potentially the site of dissemination of this fungus, leading to systemic disease (13).

C. albicans invade the epithelial barrier when its hyphal form is favored due to disturbances in the microbiota diversity, secretion of certain peptides, and the overall operations in the immune system (14). The process of translocation consists of adhesion, invasion, and damage, and all three of these stages require the fungus to express hypha-related

genes. The fungus breaches the barrier through active penetration, and *ECE1*, a gene that encodes candidalysin, is essential for fungal translocation and for causing damage to the epithelial tissue (14). Candidalysin, a cytolytic peptide toxin, mediates the translocation of *C. albicans* through multiple intestinal layers to the bloodstream, and this translocation occurs primarily due to necrotic cell death and epithelial damage (14, 15). Since this toxin is needed for both intestinal epithelial damage and translocation, *C. albicans* without the *ECE1* gene cannot translocate across the epithelial barrier because it is unable to damage and permeate the barrier. In addition, these mutants do not perform their wild-type (WT) role even with the exogenous addition of candidalysin. This particular finding implies the natural secretion of candidalysin by the hyphae is needed for damage and translocation to occur (14, 15). However, it is important to note that in some instances translocation and fungal invasions can occur without candidalysin or considerable damage to epithelial cells. This finding implies that epithelial integrity also depends on damage-independent fungal factors, such as interfering with TJs and adherens junctions, and that there is an alternative route for translocation as well, such as the paracellular route (14). Currently, scientists do not fully understand the molecular basis underlying enhanced intestinal permeability during *C. albicans* infection; specifically, JAM-A's precise role in the regulation of the epithelial barrier and intestinal translocation needs to be further investigated. Figure 4 highlights the result of perpetuating pathologic mucosal inflammation, leading to translocation of fungal cells between IECs.

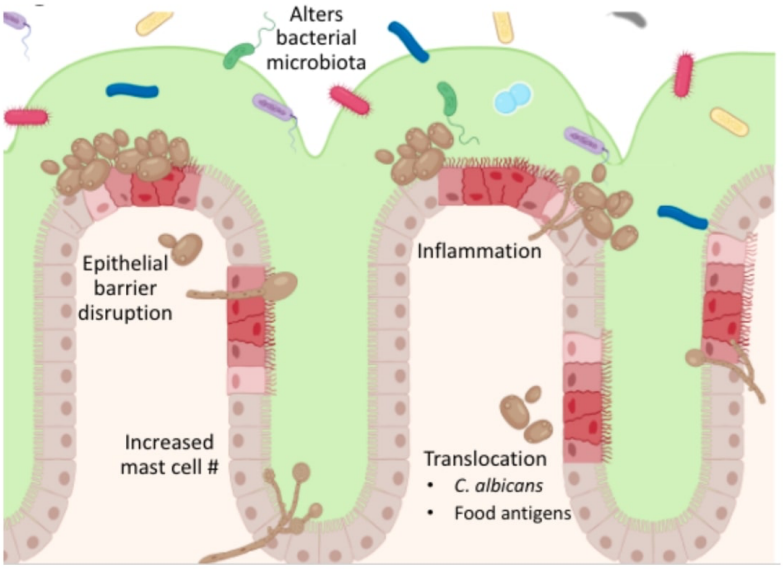

FIG. 4 Effects of a fungal invasion. *C. albicans* actively breaching mucosal epithelial tissues, resulting in bacterial microbiota alteration, inflammation, increased mast cell production, and translocation of *C. albicans* and food antigens.

IMMUNE CELL ACTIVATION

Immune cells are activated by disruption of the epithelial barrier from a *C. albicans* infection. The potential of this microbe to cause disease and activate cells of the immune system depends on host-pathogen interactions. These interactions involve pathogen virulence factors and the host immune response (16). As the innate immune system is the first line of defense, it is among the first to have direct contact with *C. albicans* infection.

Belonging to the innate arm of immunity, MCs are considered the body's first-response immune cells. They originate in the bone marrow through the myeloid lineage, travel to the bloodstream, migrate to the periphery, and differentiate into mature MCs with tissue-specific phenotypes (16). MCs reside in almost all vascularized tissues and can be exposed to external environment, such as mucosal sites. This strategic localization of MCs allows them to be among the first immune cells to respond to various allergens, pathogens, and other foreign agents following the disruption of the outer mucosal surface of the epithelial barrier (16). After a fungal invasion, MCs detect the invading fungus with various pattern recognition receptors (PRRs). The two main PRRs involved in anti-fungal infection immune response are the Toll-like receptors (TLRs) and C-type lectin-like receptors (CLRs) (17). *C. albicans'* cell

wall is composed of proteins and carbohydrate polymers, which is recognized by receptors, triggering an immune response. Early on during a fungal infection, the MC line HMC-1 degranulates, which decreases the fungal infection risk by 30% in humans. This same cell line also recruits neutrophils and releases IL-16 and IL-1ra, which are anti-inflammatory mediators (17).

Although MCs are recognized as effectors of allergic reactions and anaphylaxis, their dynamics during *C. albicans* infection are not well understood (16, 17). Therefore, studying their role in the epithelium is critical in the context of *C. albicans* infection to understand the importance of the immune response of MCs; specifically, changes in the number, location, and function of MCs during *C. albicans* infection need to be investigated.

MAST CELLS AND IL-9 ACTIVATION

The translocation of *C. albicans* past the epithelial barrier correlates with increased MC numbers and the activation of inflammatory cytokines and immune cells. MCs exhibit plasticity that can be modulated by many factors, including changes in the cytokine milieu associated with inflammatory or immune responses (16, 18, 19). Two types of MCs in mice are classified based on their phenotypic characteristics and their anatomic locations. The first is the connective tissue-type MCs (CTMCs), which primarily reside in stromal tissues around venules and nerves and are derived from fetal liver progenitors. The second and relevant type, mucosal MCs (MMCs), occupy the mucosa of the gut and lung and are of bone marrow origin (1, 20). MMCs are particularly abundant in epithelial cells and are well-positioned to respond to pathogens that disrupt the epithelial barrier (20). CTMCs and MMCs are often distinguished based on their protease content. Mouse intestinal MMCs express MC proteases-1 (MCPT-1), but CTMCs do not express MCPT-1 and instead express MCPT-4 and MCPT-6 (20).

Among MMCs, interleukin-9 (IL-9)-producing MMCs, termed MMC9s, are the primary producers of the cytokine IL-9 (11, 21, 22). MMC9s are scarcely found in the GI tracts of immunologically compromised mice and substantially expand after antigen or pathogen exposure. MMC9s amplify intestinal mastocytosis involved in food allergy, anaphylaxis, intestinal inflammation, and several mucosal inflammatory diseases (11, 21, 22). A recent role for the MMC/IL-9 axis has been demonstrated in mucosal candidiasis, whereby *Candida*-driven MMCs and the subsequent secretion of IL-9 have been shown to control *C. albicans* behavior and colonization in the GI tract (22). Several studies have highlighted the immunomodulatory roles of MMCs and IL-9 during *C. albicans* infection (11, 21). However, these experimental models lack demonstration of epithelial cell readouts, such as changes in TJ formation, that may lead to expansion of MMCs during *C. albicans* colonization. Based on these unknowns, it is imperative to study the changes in MMCs during *C. albicans* infection and the molecular mechanisms occurring in the epithelium that potentially lead to immune cell activation.

PERSPECTIVES ON ADVANCING TREATMENTS

Candidiasis can cause a wide range of diseases with varying levels of danger. For example, candidaemia only exhibits minimal symptoms; fulminant sepsis has severe symptoms and a mortality rate of over 70% (23). One of the main factors that contribute to candidiasis' inherent susceptibility to infect is that the medical community faces challenges diagnosing it in its early invasion phase (23). Obtaining an early diagnosis is key to determining an effective management plan. Research has also shown that the ongoing development of rapid molecular diagnostics could enhance detection of candidiasis during the beginning stages of infection and considerably reduce mortality rates (23).

Several malignant traits of *C. albicans*, such as morphology, secretion factors, and adherence to epithelial cells, are the main reasons behind its ability to cause opportunistic infections. Research has revealed that targeting these traits may yield promising advances in vaccine and antifungal drug development (24). By targeting these characteristics of *C. albicans*, researchers can potentially develop vaccines and antifungal treatments against *C. albicans* infections. Some scientists argue that a multivalent vaccine needs to be developed that will target multiple virulence traits of this fungal infection instead of a vaccine that aims to tackle merely the major virulence traits (25). According to these scientists, the univalent

subunit vaccines that are currently in the clinical trial phases may not be effective as they will only respond to a select number of virulence traits (25). This limited response will lead to a muted immune response as *C. albicans* infections evades the host immune system remarkably well.

The first harmful characteristic of *C. albicans* that researchers endeavor to counter is its ability to interchange among its unicellular yeast cells, pseudo-hyphae, and hyphae forms. When a given strain of *C. albicans* is in its yeast or filamentous form, it causes invasive disease in the host (24). Different environmental factors cause *C. albicans* to change shape, which plays a key role in immune evasion. Fungal sensing by the immune system of the human host is affected by the composition and exposure of surface components such as mannoproteins, glucans, and chitin in various *Candida* species morphotypes (24). Secondly, researchers plan to stem the section of several factors secreted from pathogenic *C. albicans*, which are responsible for perpetuating the fungal invasion and damaging epithelial cells (24). Studies are currently being conducted to reduce the secretion of hydrolases, which assists fungal infections in the active penetration of the epithelial barrier (2). The final trait being combatted is *C. albicans'* ability to be thoroughly disseminated in the host bloodstream due to its strong adherence to epithelial cells.

DISCUSSION

C. albicans is the most common human fungal pathogen and is implicated in intestinal diseases. Although the intestinal epithelium establishes a selective barrier against pathogens, *C. albicans* can breach the barrier, causing damage and increase intestinal permeability. The molecular changes occurring in the epithelium during *C. albicans* infection have not been studied; however, several reports link regulation of the epithelial barrier to JAM-A (8). Therefore, it is critical to study the role of JAM-A during *C. albicans* infection. When *C. albicans* invades through epithelial cells, MCs are resident tissue sentinels that are among the first immune cells to interact with the fungus. MCs are strongly implicated as key players of *Candida* pathogenicity at mucosal surfaces (1). The activity of MCs during *C. albicans* infection is not well understood as they are often known only for being effectors of allergic reactions and anaphylaxis. Therefore, studying their role in the epithelium during *C. albicans* infection is crucial. Based on this rationale, it can be assumed that *C. albicans* infection results in changes in epithelial barrier formation, specifically JAM-A, followed by mucosal MC activation. This assumption is based on the following three proven facts: *C. albicans* colonization in the gut has been shown to enhance intestinal permeability, JAM-A regulates epithelial barrier function and intestinal permeability, and MMCs participate in *C. albicans*-host interactions at mucosal surfaces (1, 8).

To expand on this hypothesis, it is essential to determine molecular changes in the gut epithelium that accompany *C. albicans* infection. Since recent data has demonstrated a role for JAM-A in regulating the epithelial barrier, scientists should plan to intragastrically inoculate WT and JAM-A-deficient mice with *C. albicans* and set-up in vivo experiments to uncover the molecular pathways causing epithelial changes and enhanced intestinal permeability (8). The working hypothesis in the science community should be that *C. albicans* infection results in a defect in JAM-A, consequently disrupting the epithelial barrier and increasing permeability.

After setting-up this experiment based on this hypothesis, microbiologists must delineate the changes in MCCs accompanying *C. albicans* infection. MMCs are among the first responders to *C. albicans* infection and play a role in mucosal candidiasis (18, 19). Using a combination of techniques including flow cytometry, MC staining, enzyme-linked immunosorbent assay (ELISA), and reverse transcription polymerase chain reaction (RT-PCR), microbiologists need to assess changes in MMC number, function, and location in response to *C. albicans* infection. To determine how MCs solely interact with *C. albicans*, these scientists also must cultivate bone marrow-derived mast cells (BMMCs) and set up cell cultures to study the temporal response of MCs to *C. albicans* in vitro. The hypothesis for this part of the experiment should be that MC activation and recruitment increases in the epithelium upon fungal interaction, which leads to MC degranulation and secretion of cytokines and proteases, like IL-9 and MCPT-1, respectively (10, 20). It is also essential to determine changes in mucosal mast cells that accompany changes in epithelial TJ formation,

specifically in JAM-A. The role of alterations in TJ formation, particularly JAM-A, on the changes in MMCs needs to be further investigated. Using JAM-A-deficient mice, similar experiments need to be performed to reveal changes in MCs in the mucosal epithelium. The working hypothesis should be that changes in TJ formation leading to increases in MMC activation and recruitment.

Because yeast-host interactions in the gut is not well studied, the data from this proposed study will provide a newfound understanding of how mucosal *C. albicans* infection impacts the molecular components of the gut epithelium and consequently activates cells of the immune system. This will not only benefit the scientific community, but it will also contribute to improving human health and understanding diseases in the medical field as well.

CONCLUSIONS AND FUTURE PERSPECTIVES

The GI tract hosts most of the *C. albicans* community and connects directly to the bloodstream, increasing the potential for an infection to spread. Breaching of the mucosal epithelial barrier causes an increase in the number of MCs being activated. The model of *C. albicans* invasion and immune activation in the GI tract is not well studied, exemplifying the need for future research explaining MC activation in the GI tract.

Yamaguchi et al., Chen et al., and other groups have studied the epithelial barrier function and enhanced GI permeability in relation to inflammatory diseases and food allergies (11, 13). Although *C. albicans* colonization has also been associated with epithelial barrier impairment, the molecular basis underlying enhanced intestinal permeability during *C. albicans* infection is not currently understood. Given the established correlations between epithelial barrier function, enhanced GI permeability and *C. albicans* infection, further research is needed to uncover the molecular basis for this intestinal permeability during candidiasis.

Furthermore, there are also factors at the microbial level that can affect *C. albicans* colonization and disease outcomes. Secretion of candidalysin damages epithelial cells and activates immune cell activation in the oral mucosa (26). In turn, further research is needed to study candidalysin to observe its activity and role in the GI tract. *C. albicans* infection has been reported to regulate the bacterial microbiome whereby bacteria-related interactions may contribute to epithelial changes and gut inflammation. For example, the risk of fungal urinary tract infections increases when *Escherichia coli* interacts with *C. albicans* to increase the fungal adhesion in the bladder mucosa area (27). Also, co-infection by both *C. albicans* and *Staphylococcus aureus* leads to increased mortality (27). Additional research is needed to monitor the effects of bacterial secreted products on the host epithelial environment and immune activation (27).

Currently, quality of life studies have not been performed on survivors of invasive candidiasis. Such studies are needed to inform medical practitioners of the efficacy of the treatments and to inform their future treatment plans. Furthermore, the main challenges to the management of invasive candidiasis include prevention, early recognition of invasion, and subsequent rapid initiation of antifungal therapy. Blood cultures, microscopic examinations, biochemical identification, polymerase chain reaction (PCR), real-time PCR, mass spectrometry, and immunoassay are a few examples of early detection methods. However, these methods are flawed as they are time-consuming, expensive, and may not produce accurate results in some cases (28). These factors lead to a delay in anti-fungal treatment plans, which may prove to be detrimental to patients. Polymerase spiral reaction (PSR) assays are an alternative way to detect early fungal infections that is favored by the science community due to these assays' quick and accurate results (28). Performed under isothermal conditions, the PSR takes less than an hour to produce results and has a 94.1% sensitivity rate, indicating its readiness for clinical testing (28). More research in this field should focus on earlier diagnosis techniques by non-culture-based molecular tests and on strategies that emphasize early intervention.

ACKNOWLEDGEMENTS

I want to thank and acknowledge my mentor, Malak H. Bazzi, a PhD candidate at the University of Michigan, for overseeing this review paper and helping me find relevant research articles on my topic and for editing my paper. I would also like to acknowledge the Lumiere Research Scholar Program for admitting me into their program, which enabled me to write this paper and get into contact with Malak. We would also like to thank two anonymous reviewers for constructive feedback on this manuscript.

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