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Candida albicans infection and intestinal immunity

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ABSTRACT

Fungal infections cause high rates of morbidity and mortality in intensive care and immunocompromised patients, and can represent a life-threatening disease. As a microorganism commonly found in the intestine, *Candida albicans* (*C. albicans*) can invade the gut epithelium barrier via microfold cells and enter the bloodstream. The defensive potential of the intestinal barrier against invasive *C. albicans* is dependent on innate and adaptive immune responses which enable the host to eliminate pathogenic fungi. The lamina propria layer of the intestine contains numerous immune cells capable of inducing an innate cellular immune response against invasive fungi. This review focuses on the immune response triggered by a *C. albicans* infection in the intestine.

Contents

1. Introduction

Fungal infections have become an increasingly important type of nosocomial bloodstream infection, and are particularly common among critically ill and intensive care patients, as well as in patients with a solid malignancy or who are recovering from abdominal surgery (Pongracz et al., 2015; Li et al., 2016b). While *Candida albicans (C. albicans)* is a normal constituent of human intestinal (Brown et al., 2012), oral cavity, and vaginal microflora, it is also the major cause of nosocomial fungemia. Many *C. albicans* infections result from the use of indwelling medical devices, such as intravenous lines, catheters, and drains. These devices bypass the physicalbarrier provided by the mucosal surface, and facilitate the access of microorganisms to the bloodstream (Richardson and Moyes, 2015). In some susceptible individuals, *C. albicans* infections are thought to disseminate from the gastrointestinal tract; this hypothesis is supported by data obtained from studies in both patients and animal models (Miranda et al., 2009; Maraki et al., 2015; Shankar et al., 2015). *C. albicans* can cause a life-threatening illness with significant rates of mortality in immunocompromised patients as well as in patients receiving immunosuppressive therapy (Pongracz et al., 2015). *C. albicans* is the most common fungal pathogen found in intensive care unit patients and causes infections which can lead to severe sepsis and septic shock, both of which are associated with high rates of morbidity and mortality, and eventually contribute to an increase of health care costs on a global basis (Martin et al., 2002; Kollef et al., 2012; Doi et al., 2016; Si et al., 2016). With the exception of primary infections, sepsis and invasive

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infections caused by *C. albicans* always occur as complications of bacterial sepsis resulting from concomitant immune paralysis. The treatment of these secondary *C. albicans* infections often requires a prolonged ICU stay, which results in additional financial costs (Xie et al., 2008). This review article focuses on recent advances in our understanding of the role that immunity plays in the pathogenesis *C. albicans* intestinal infections.

2. Mucins and M cells: important factors for *C. albicans* entry

The intestinal mucosal barrier plays an important role in the protection against an invasion of pathogens and their overgrowth and translocation to deep organs. Three important factors contribute to the occurrence of an intestinal invasion of *C. albicans*: (1) the lack of an effective host immune response; (2) intestinal dysfunction resulting from an intestinal flora disorder, permeability changes, or a break in the intestinal barrier; (3) a change in *Candida* morphology (Yan et al., 2013). Certain mucin glycoproteins, anti-microbial peptides, and secreted immunoglobulins (SIgA and IgG) in the small intestine are involved in the defense against pathogens. Some of the mucins produced by goblet cells in the GI tract have antifungal effects. For example, MUC2 in pig intestinal mucus and MUC5 in pig gastric mucus inhibit the growth of *C. albicans* via several different mechanisms, including through control of the physiological processes and downregulation of the virulence-associated genes in *C. albicans*, as well as by decreasing its biofilm formation and suppressing the transition of the pathogen to a filamentous state and its surface adhesive capability (Kavanaugh et al., 2014). However, this fungus has been shown to degrade small-intestinal mucin *in vitro* via endogenous aspartyl protease (Colina et al., 1996).

Microfold cells (M cells) are found in the gut-associated lymphoid tissue (GALT) of Peyer's patches and the mucosa-associated lymphoid tissue (MALT) of other parts of the gastrointestinal tract devoid of mucin. These cells are known to facilitate the translocation of mucosal antigens across the intestinal barrier and the following induction of an appropriate immune response in Peyer's patches. Therefore, M cells serve as immunosurveillance receptors for pathogens in the gut (Mabbott et al., 2013). A recent study showed that *C. albicans* can use M cells as a portal of entry to cross the epithelial barrier. Moreover, F-actin-dependent endocytosis contributed to the translocation of *C. albicans* into M cells via hypha-specific surface proteins, such as Ssa1 and Als3 (Albac et al., 2016). The efficient M-cell-mediated sampling of antigens in the gut lumen antigens is considered an important initial step in the induction of certain mucosal immune responses (Lelouard et al., 2012; Mabbott et al., 2013).

3. Immune recognition of *C. albicans* by pattern-recognition receptors (PRRs)

The fundamental purpose of host innate immunity is to distinguish self from non-self (pathogen) agents. The cell wall of *C. albicans* contains three types of target molecules (chitin, glucans, and mannans) providing pathogen-associated molecular patterns (PAMPs) that can be recognized by the host immune system with and trigger an immune response. Chitin and β-glucan form hydrogen bonds with each other to construct a tough 3-dimensional inner-layer network of microfibrils. The outer layer is composed of O- and N-linked mannans attached to highly glycosylated cell wall proteins (Nather and Munro, 2008; Mora-Montes et al., 2011; Machova et al., 2015). However, some other intracellular components, including certain DNA and RNA molecules, also display PAMPs (Miyazato et al., 2009) (Müller et al., 2007). Polysaccharide structures of the cell wall of *C. albicans* are recognized by four classes of pattern recognition receptors (PRRs): (1) Toll-like receptors (TLRs), (2) C-type lectin receptors (CLRs), (3) nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and (4) retinoic-acid-inducible gene I (RIGI)-like receptors (RLRs) (Netea et al., 2008; Zheng et al., 2015). The first PRRs discovered to recognize *C. albicans* were found belong to the TLR family. Since then,13 TLRs have been identified in both humans and mice. The majority of TLRs are expressed at the mRNA level in the human colon and small intestine. However, our knowledge concerning their distribution in the epithelium, their cell specificity, and how they distinguish between symbiotic and pathogenic organisms is incomplete. Human mucosal epithelial cells have been proven to express TLR1, TLR2, TLR3, TLR4, TLR5, and TRL6 (Saegusa et al., 2004; Furrie et al., 2005; Bahri et al., 2010), whose main role is to initiate a host defense response. However, the location and function of TLR family members in the intestine are unique due the presence of commensal bacteria in the gut (Uematsu and Fujimoto, 2010). TLR2 can recognize phospholipomannan (PLM) (Jouault et al., 2003), whereas TLR4 can recognize not only O-linked mannans, but also mannan (Netea et al., 2006; Kawai and Akira, 2010). TLR2 and TLR4 have essential functions in the immune recognition of a *C. albicans* infection. TLR2 and TLR4 are expressed at low levels by intestinal epithelial cells in normal human colon tissue but are overexpressed in crypt epithelial cells (Abreu et al., 2001; Furrie et al., 2005; Wells et al., 2011). TLR2 and TLR4 were found to be localized on the follicle-associated epithelium (FAE) and the epithelium of small-intestinal villi and crypts in a mouse model (Chabot et al., 2006). A recent study showed that TLR2 may contribute to the protection against the colonization and endogenous invasion by *C. albicans* (Prieto et al., 2016). TLR3, TLR7, and TLR9 function as endosomal receptors. TLR3 recognizes double-stranded RNA (Müller et al., 2007), whereas TLR9 directly distinguishes CpG DNA (Miyazato et al., 2009), and TLR7 specifically identifies the single-stranded RNA of *C. albicans* (Wells et al., 2011; Biondo et al., 2012). TLR3 appears to be abundantly expressed only in the mature enterocytes of normal human small intestine and colon tissue (Cario et al., 2000).

The second major PRR family known to recognize *C. albicans* PAMPs is the C-type lectin receptor (CLR) family. Members of the CLR family, including dectin-1, dectin-2, DC-specific ICAM3-grabbing non-integrin (DC-SIGN), galectin-3, mincle, and the mannose receptor, have been reported to collectively recognize *C. albicans* cell wall components, such as mannan (Cambi et al., 2008), β-glucans (Brown et al., 2002), (McGreal et al., 2006), high-mannose (Saijo et al., 2010), N-linked mannan (Netea et al., 2006), and β-(1,2)-mannosides (Jouault et al., 2006). In particular, dectin-1 recognizes β-glucans and stimulates the production of pro- and anti-inflammatory cytokines to trigger an immune response in human intestinal epithelial cells (IECs) (Taylor et al., 2006; Cohen-Kedar et al., 2014). *C. albicans* yeast cells display their β-glucan motif on the cell wall, whereas the hyphae of *C. albicans* hide their β-glucan residues beneath a cover of mannoproteins. This molecular arrangement allows *C. albicans* to escape dectin-1-mediated phagocytosis (Taylor et al., 2006). Dectin-1 is essential for the control of systemic infections rather than for the regulation of gastrointestinal colonization by pathogens (Vautier et al., 2012). Mannan-binding lectin (MBL) is a soluble CLR produced by the liver which opsonizes phagocytes by binding to *C. albicans* mannan residues and the C1q receptor (Sealy et al., 2008; Moslem et al., 2015). A recent study showed that MBL expression was induced in the gut in response to sensing the presence of *C. albicans* and was required for intestinal homeostasis and host defense (Choteau et al., 2016). Belonging to the Nod-like receptor (NLR) family, NLRP3 and NLRC4 proteins play important roles in defending the host against a *C. albicans* infection (Hise et al., 2009; Tomalka et al., 2011). Inflammasome formation is partly initiated by activation of nod-like receptor proteins (NLRP1,