

# Candida Infection Pathogenesis and Host Defensive Mechanism

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## Abstract

Candida is a Gram-positive spherical fungi facultative anaerobe, has more than 17 different species and classified into *C. albicans* and non *albicans* species. Host response to Candida infection is a complex interplay between innate and adaptive immunity and usually provides a sufficient defense against microbes in healthy individuals but not in immunocompromised ones. Cytokines produced from immune cells also play an important role in epithelial immunity against Candida infection. Candida infection is established by many mechanisms as Adhesins, Invasins, Biofilm, aspartyl proteinases - Haemolysins and Phospholipases.

**Keywords:** Candida; PRRs; TLRs; GM; CSF; Adhesins; Invasins; Biofilm; Aspartyl Proteinases; Haemolysins; Phospholipases

## Introduction

Candida is a Gram-positive spherical fungi approximately 3  $\mu\text{m}$  in diameter. Its cells form budding appearance, since cell division takes place in more than one plane. It is often found as a commensal associated the skin and mucosal surfaces of humans [1].

On an enriched medium, Candida forms variable size white colonies according to species. On sheep blood agar plates, colonies often cause  $\beta$ -hemolysis due to secretion of hemolysin. Candida is facultative anaerobe capable of generating energy by aerobic respiration, and by fermentation which yields mainly lactic acid [2].

Critically ill or otherwise immunocompromised patients as diabetics, HIV infected individuals and who

are under massive antibiotics therapy are more prone to develop both superficial and life-threatening Candida infections [1].

## Classification

Candida can be classified as the followings:

Kingdom: Fungi

Phylum: Ascomycota

Subphylum: Saccharomycotina

Class: Saccharomycetes

Order: Saccharomycetales

Family: Saccharomycetaceae

Genus: Candida and more than 17 different species are known to be etiological agents of human infection.

*Candida* species classified into *C. albicans* and *non albicans* species [3].

### Host Defense Mechanisms against *Candida*

Host response to *Candida* infection is a complex interplay between innate and adaptive immunity and usually provides a sufficient defense against microbes in healthy individuals but not in immunocompromised ones. First, pathogen related receptors (PRRs) are expressed by cells of the innate immune system and specific immunity to recognize pathogen-associated molecular patterns (PAMPs), which are structural components characteristic for microbial pathogens. Recognition of PAMPs leads to microbial uptake and, consecutively, to a modulation of gene to initiate an adaptive and target-oriented immune response [4].

Three main groups of PRRs have been distinguished: toll-like receptors (TLRs), C-type lectin receptors (CLRs) and nucleotide-binding domain leucine-rich repeat containing (NLR) protein family. Each ligand-receptor

system activates specific intracellular signaling pathways. *Candida* cell wall components are mainly recognized extracellularly by Toll-like receptors as in Figure 1 and C-type lectin receptors on the host cell surface [5].

Mucosalepitheliumisthe first line of defense against *Candida* species. Epithelial cells express most of the toll like receptors (TLRs), with the exception of TLR5 and TLR7, to recognize invading microorganisms [6]. Recognition of *Candida* by TLRs leads to different downstream signaling, such as Chemokine/cytokine production and phagocytosis. Once *Candida* is internalized and phagocytosed, the fungal PAMPs can further activate TLR9 [4].

Polymorphonuclear neutrophils (PMNs) are believed to be the most effective cell type for controlling and clearing *Candida* infection. In addition to their direct killing of *C. albicans*, it was demonstrated that PMN sare the only cell type in blood which can inhibit *C. albicans* germ tube formation [7].

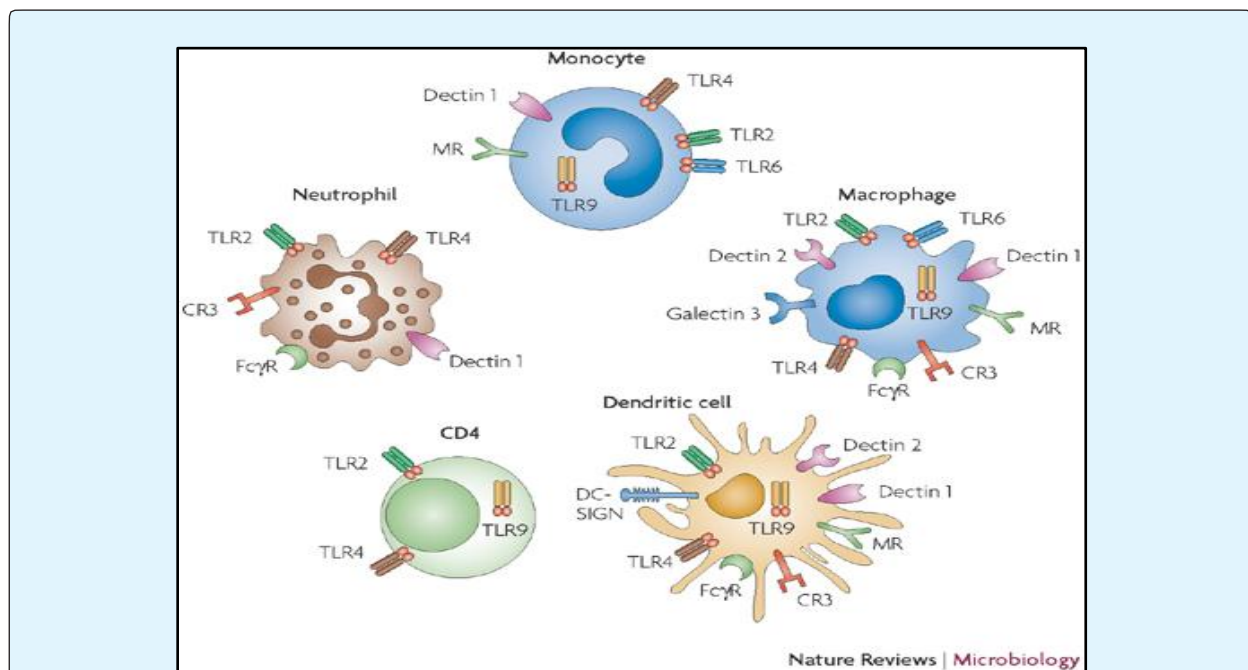


Figure 1: Cell populations and pattern-recognition receptors involved in *Candida albicans* recognition [5].

Cytokines produced from immune cells also play an important role in epithelial immunity against *Candida* infection. Several pro-inflammatory cytokines, such as IL-6, IL-8, IL-17 and TNF, have been reported to be responsible for the recruitment of PMNs to the site of

infection. In addition to pro-inflammatory cytokines, the hematopoietic growth factors granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are critical for recruitment and activation of PMNs [4].

Dendritic cells as professional antigen-presenting cells, DCs reside and patrol in the skin and mucosal surface, and they ingest *Candida* once tissues are invaded. *Candida species* are internalized by DCs [8], leading to the processing and presentation of *Candida* specific antigens via major histocompatibility complex (MHC) class II molecules. DCs discriminate between yeast- and hyphal phase forms of *C. albicans* and induce T helper cell differentiation [4].

Ingestion of yeasts primes T helper type 1 cells (Th1), whereas ingestion of hyphae inhibits IL-12 and Th1

differentiation, favoring Th2 differentiation. Thus, DCs bridge the innate and adaptive antifungal responses by recognizing different morphologies of *Candida* [4].

### Candida Pathogenesis

#### Adherence to Host Tissue

Adherence is essential for members of the genus *Candida* to develop their pathogenic potential, since it triggers the process that leads to colonization and allows their persistence in the host tissue invasion as shown in Figure 2 [9].

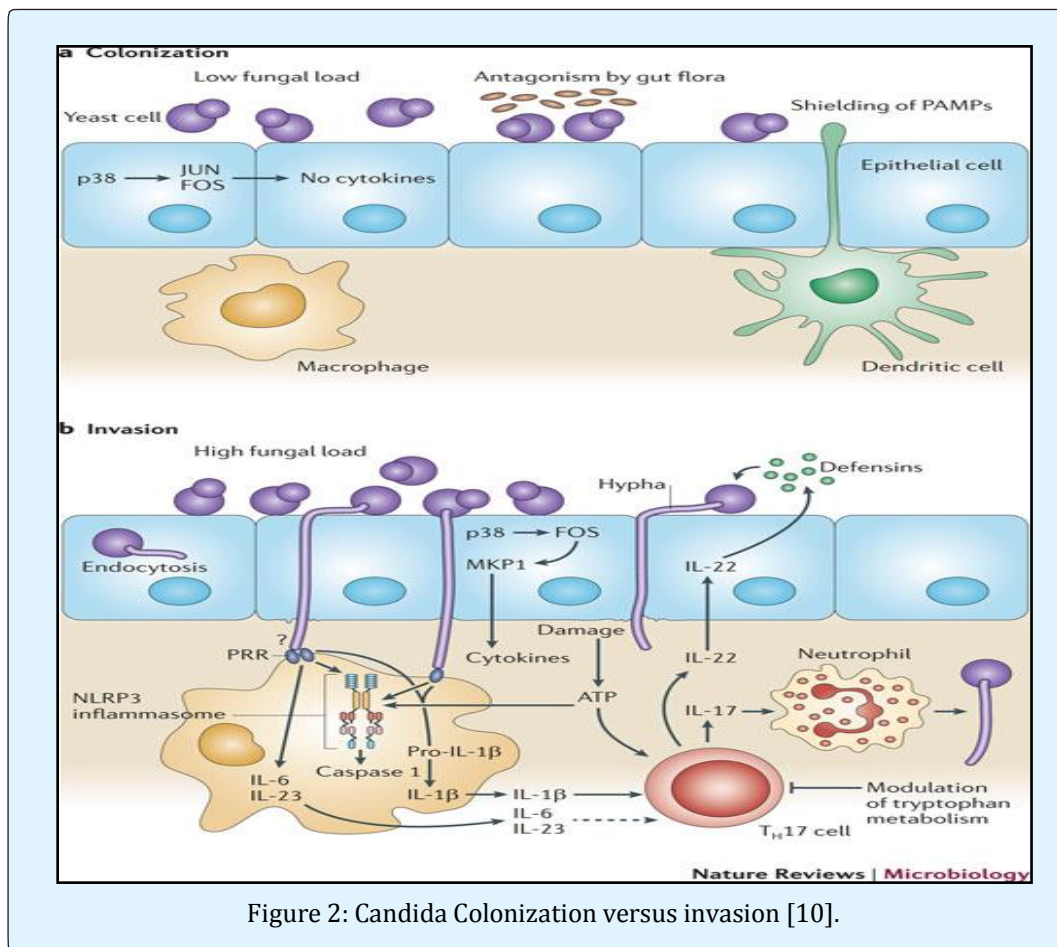


Figure 2: *Candida* Colonization versus invasion [10].

Different intra-species adherence ability has been reported for *Candida* species [9]. For instance, adherence of *C. albicans* to epithelial cells is greater than that of *C. parapsilosis* [11]. *C. tropicalis* exhibited higher ability to colonize reconstituted human epithelium (RHE) than did *C. parapsilosis* and *Candida glabrata* [12]. Adherence can be mediated through two families of enzymes including adhesins and Invasins.

#### Adhesins

*C. albicans* has a specialized set of proteins (adhesins) which mediate adherence to other *C. albicans* cells, to other microorganisms, to a biotic surface and to host cells. The best studied *C. albicans* adhesins are the agglutinin-like sequence (ALs) proteins which form a family consisting of eight members (ALs1–7 and ALs9). The ALs genes encode glycosylphosphatidylinositol (GPI)-linked

cell surface glycoproteins. Of the eight ALs proteins, the hypha-associated adhesin Als3 is especially important for adhesion [13].

The agglutinin-like sequence (Als3) gene expression is up regulated during infection of oral epithelial cells in vitro and during in vivo vaginal infection [14]. Another important adhesin of *C. albicans* is Hwp1, which is a hyphae-associated GPI-linked protein. Hwp1 serves as a substrate for mammalian transglutaminases and this reaction may covalently link *C. albicans* hyphae to host cells [15].

### Invasins

*C. albicans* is a remarkable pathogen as it can utilize two different mechanisms to invade into host cells: induced endocytosis and active penetration [16].

For induced endocytosis, the fungus expresses specialized proteins on the cell surface (Invasins) that mediate binding to host ligands (such as E-cadherin on epithelial cells and N-cadherin on endothelial cells), thereby triggering engulfment of the fungal cell into the host cell [14].

Indeed, even killed hyphae are taken up, indicating that induced endocytosis is a passive process that does not require the activities of viable fungal cells. Two invasins have been identified so far, namely Als3 (The agglutinin-like sequence (Als3) (which also functions as an adhesin) and Cell-surface expressed member of the heat shock protein 70 (Hsp70) family (Ssa1) which present on the surface of hypha and plays synergistic role with Als3 [14].

Adhesion between *Candida* species cells and host cells has been implicated as an early step in biofilm formation [1].

### Biofilm

Biofilms are specific and organized communities of cells under the control of signaling molecules, rather than random accumulations of cells resulting from cell division. *C. albicans* in a biotic surface biofilms consists of two general types of cells: yeast cells and filamentous cells [17].

In vitro, the basal biofilm layer is composed of yeast cells from which filamentous cells emanate. In *Candida* the dimorphic transition from the yeast to the hyphal phase is a crucial step in the formation of biofilms, and mutant strains that are defective in the ability to germinate are unable to form dense and homogeneous biofilms [18].

These yeast and filamentous cells are embedded in a dense layer of extracellular matrix that is self-produced and formed of carbohydrates, proteins, phosphorus and hexosamines. The primary component of biofilm matrix is B-glucan [17].

Environmental conditions such as medium composition, pH and oxygen as well as the fungal strain and species affect biofilm formation and matrix composition. For example, *C. parapsilosis* biofilms contain large amounts of carbohydrates, and the protein content is low when compared with biofilms of *C. glabrata* and *C. tropicalis* [9].

Biofilms can grow on any biotic or a biotic moist surface. The association of organisms in biofilms is a form of protection for their development, encouraging symbiotic relationships and allowing survival in hostile environments [18]. Biofilms may help maintain the role of fungi as pathogenic by evading host immune mechanisms, resisting antifungal treatment and withstanding competitive pressure from other organisms. Biofilm formation by fungi may play an important role in pathogenesis [19]. These biofilms help mixed bacterial and fungal infection found in vaginal infections by *Candida* species and *Gardnerella vaginalis* [20].

Recent evidence suggests that the majority of disease produced by *C. albicans* is associated with biofilm growth [21].

### Secreted Hydrolytic Enzymes

The secretion of hydrolytic enzymes during infection is required as a virulence factor to aid adhesion, invasion, and the destruction of host immune factors, in addition to nutrient acquisition. These enzymes include secreted aspartyl proteinases (SAP), Haemolysins and phospholipases (PL) [22].

### Secreted Aspartyl Proteinases

Secreted aspartyl proteinases (Sap), encoded by a 10-members of gene family (*SAP1 to SAP10*) have been the most extensively studied. The 10 *SAP* genes that compose this family can be divided into subfamilies based on amino acid sequence homology alignments (*SAP1 to SAP3*, *SAP4 to SAP6*, *SAP9*, and *SAP10*). These genes exhibit differential expression profiles at different stages and sites of infection [22].

Sap2 is the most highly expressed secreted protease in vitro and is capable of digesting human albumin, hemoglobin, keratin, and secreted immunoglobulin A.

Sap2 is believed to allow *C. albicans* to destroy host barriers through the degradation of human proteins, followed by deep penetration into tissues or the bloodstream. In addition, Sap2 digests extracellular proteins into oligopeptides that can be taken up by oligopeptide transporters encoded by the OPT gene family. Therefore, Sap2 may also be critical for cell growth in the human host and may enable the use of host proteins as a nitrogen source. Sap1to-6 played limited roles in *C. albicans* virulence [4].

### Haemolysins

Haemolysins are protein produced by micro-organisms to destroy red blood cells for production of iron which is essential for the development of micro-organisms, including yeasts, and the ability to obtain this element is essential for the establishment of an infectious process [1].

### Phospholipases

The family of phospholipases consists of four different classes (A, B, C and D). Only the five members of class B (PLB1-5) are extracellular and may contribute to pathogenicity via disruption of host membranes [14] as they catalyze the hydrolysis of phospholipids, which are major components of all cell membranes [23].

### Phenotypic and Morphological Switching

*Candida* has the remarkable ability to grow in several distinct morphological forms: yeast, hyphae, and pseudohyphae, according to environmental conditions the true hyphae and pseudohyphae (chains of elliptical cells with constrictions at the septa) are often referred to as filamentous forms. The ability to switch rapidly from yeast-to-filamentous growth or vice versa in response to certain environmental factors is considered to be a critical virulence factor for these fungi. In *C. albicans*, each morphology is believed to confer discrete advantages in the course of infection. The yeast form is important for dissemination through the bloodstream and adheres to endothelial surfaces. The filamentous forms, on the other hand, are more adapted for invasion through the host epithelial tissue and also have a higher resistance to phagocytosis due to their morphology [24].

*Candida albicans*, strains lacking hyphal formation exhibited lower ability to invade tissue compared with wild-type strains [12].

Indeed, an engulfed *C. albicans* yeast cell can destroy a macrophage if filamentous growth is triggered after phagocytosis, and filamentous forms have a higher resistance to neutrophil killing. The morphogenesis of *C.*

*albicans* is predominately determined by environmental signaling. The yeast to filamentous transition can be triggered by serum, proline, N-acetylglucosamine, different carbon sources [24].

*Candida parapsilosis* does not form true hyphae and exists in either a yeast phase or a pseudohyphal form. Differently, *C. tropicalis* can exist in multiple morphogenetic forms, including yeast phase, pseudohyphae and true hyphae, being considered polymorphic fungi [12].

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