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Candida albicans infection: Virulence factors and pathogenesis

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Abstract

There are over 100 species in the genus *Candida*, however only few of them are harmful to humans. A widespread commensal fungus called *Candida albicans* colonizes the skin of healthy people, the gastrointestinal and vaginal tracts, and the oropharynx, especially in immunocompromised people. *C. albicans* is a normal component of the microbiota's flora in 50% of the population. *Candida* can present with a wide range of clinical symptoms before developing into an opportunistic infection. These symptoms might include localized, superficial mucocutaneous problems or invasive, potentially fatal diseases involving several organ systems. The expression of virulence factors like adhesins and invasins, the secretion of hydrolytic enzymes, the transition from yeast (at 37°C) to filamentous hyphae (molds) (at 22°C), and the capacity to form biofilms are characteristics of the interaction between *Candida albicans* and host cells. These characteristics taken together lead to cell adhesion, invasion, and damage. Several virulence factors that contribute to disease are expressed by *Candida albicans*. These include morphogenesis (the reversible change between unicellular yeast cells and filamentous, growing forms), secreted aspartyl proteases, and phospholipases. Host recognition biomolecules include adhesins. Primary and secondary candidiasis is the two categories of oral candidiasis, which have different clinical presentations. The gastrointestinal tract serves as the body's primary source of *Candida albicans*, and immune system malfunction, mucosal barrier degradation, and dysbiosis of the home microbiota all contribute to the development of infections. *Candida* infections that cause invasive candidemia are linked to the prevalence of *Candida albicans* in the blood.

Keywords: *Candida albicans*, immune, infection, candidiasis, virulence factors

Introduction

Fungal infections are a well-known indicator of compromised immunity. Numerous microorganisms with a wide range of traits make up microscopic fungus. A few numbers of them, particularly in immunocompromised patients, can infect humans and cause disease ^[1, 40]. Due to their high associated mortality and low cost, opportunistic invasive fungal infections have drawn the attention of public health systems worldwide ^[2, 3]. Fungal infections can impact the skin, nails, respiratory system, and internal organs. They are caused by a variety of fungi, including *Cryptococcus*, *Candida*, *Aspergillus*, and *Dermatophytes*. These infections are a serious health concern since they can range from superficial, moderate illnesses to severe systemic disorders. In order to effectively manage these infections, prompt identification and proper antifungal treatment are essential, particularly for those with weakened immune systems.

The most prevalent fungi that infect people are species of *Candida*. These species are real opportunistic pathogens; they enter the circulation and deep tissues by taking advantage of the host's compromised state. There are over 100 species in the genus *Candida*, however only few of them are harmful to humans. A serious infection in immunocompromised hosts, candidiasis is caused by *Candida albicans* and infrequently by other species. Numerous pathogens, including *Candida albicans*, can cause fungal infections. They can damage the skin and mucosal surfaces and can infect the entire body. Up to 400,000 different types of systemic fungal infections are caused by species of *Candida* ^[4]. Approximately 70% of fungal infections worldwide are caused by *Candida albicans*, which is the most frequent causal agent of systemic and mucosal infections worldwide ^[5]. For the previous few decades, it has been the main cause of invasive infections that can be fatal.

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The death rate is about 40% even with treatment, particularly in hospital settings ^[6, 7]. There are various morphological forms of *Candida albicans*, including blastospores, pseudohyphae, and hyphae. By budding, blastospores divide asexually ^[8]. On the surface of the blastospore, new cell material forms during that process. The new bud, which starts the growth phase, develops from a tiny, carefully chosen blastospore and is typically found away from the location of a birth scar. Cells divide when the growth phase is over, with the daughter cell forming a partition to keep itself apart from the parent cell ^[9]. Pseudohyphae are made up of chains of elongated yeast cells, while hyphae are made up of branched chains of tubular cells that do not narrow at the septation sites ^[10]. Higher than 37°C temperatures, an alkali pH, serum, and high CO₂ concentrations all promote filamentation ^[11]. In the same way, when N-acetylglucosamine (GlcNAc) is present, it is also improved by a deficiency of carbon and nitrogen ^[12]. Numerous transcription factors are among the complex regulatory network of signal pathways that are activated during this blastospore-to-hypha transition ^[13]. The primary distinction in composition between yeast and hyphae is that the hypha wall contains somewhat more chitin than yeast ^[14]. Chitin, protein, and glucan comprise the cell wall. Its function is to shield the cell from environmental stressors such osmotic shifts, dehydration, and temperature swings as well as from the host's immune system ^[15, 16]. Sterols are found in the cell membrane of fungus and are unique to them. It is produced on lipid bodies and the endoplasmic reticulum ^[17]. There is a phospholipid bilayer in the cell membrane that contains proteins that function as receptors as well as those that are involved in signal transduction and transport ^[18]. *Candida albicans* employs amino acids as a supply of nitrogen and glucose as a source of carbon in its metabolism ^[19]. This study's main goals are to compile the most recent information on *Candida albicans* virulence factors and investigate the connection between these factors and infection symptoms.

Characteristics of *Candida* species

Taxonomy

- **Kingdom:** Fungi
- **Phylum:** Ascomycota
- **Class:** Saccharomycetes
- **Order:** Saccharomycetales
- **Family:** Saccharomycetaceae
- **Genus:** *Candida*
- **Species:** *Candida albicans*

Properties

The fungus *Candida albicans* demonstrates the following characteristics:

1. **Dimorphism:** May be present in hyphal or yeast forms.
2. **Commensalism:** Usually exists on human mucous membranes and skin innocuously.
3. **Pathogenicity:** May induce infections in immunocompromised people, varying in severity.
4. **Adhesion:** Able to stick to surfaces and cells of the host, allowing for invasion and colonization.
5. Capable of forming complex biofilms that shield it from host immunological reactions and antifungals.
6. **Enzyme secretion:** Generates lipases, phospholipases, and proteases, all of which aid in tissue invasion and injury.

7. **Variation in antigen:** Able to alter surface antigens to avoid identification by the host immune system.
8. **Phenotypic switching:** Capable of alternating between GUT, opaque, and white phenotypes in order to adapt to various circumstances.
9. **Resistance:** Able to grow resistant to antifungal medications like echinocandins and azoles.
10. **Virulence factors:** Contains toxins, adhesins, and invasins, among other virulence factors.
11. **Tolerance for temperature:** Able to grow in temperatures between 20°C and 42°C.
12. **pH tolerance:** Grows in 4.5 to 8.5 pH range.
13. **Flexibility in terms of nutrients:** Able to use different sources of nitrogen and carbon.
14. **Cell wall composition:** consists of mannans, beta-glucans, and chitin in its cell wall.
15. Due to these characteristics, *Candida albicans* may grow in a variety of settings, adjust to shifting circumstances, and infect hosts that are vulnerable.

Various morphogenesis

Although *Candida albicans* is a single type of fungus, it can take on a variety of shapes or morphologies, such as:

1. **Form of yeast:** an oval-shaped single-celled organism that procreates by budding.
2. **Pseudohyphal form:** A multicellular filamentous form with a yeast cell-like chain resemblance.
3. **Hyphal form:** A real filamentous form with lengthy filaments that branch out.
4. **Chlamydospore form:** A resting cell shape with robust walls that can withstand abrasive environments.

Apart from these physical variations, *Candida albicans* has the ability to transition between distinct phenotypic states, such as:

1. **White form:** The morphology of a smooth, white colony.
2. **Opaque form:** The morphology of a rough, grayish-white colony.
3. **The GUT:** (Gastrointestinal tract) form is a unique variation designed to endure in the GI system.
4. Because of its ability to adapt to varied habitats and host niches, *Candida albicans* can exist in a variety of forms and states, which increases its virulence and capacity to cause disease.

Pathogenesis

Virulence factors of *Candida albicans*

A number of virulence factors that *Candida albicans* carries enhance its capacity to spread infection and disease:

1. **Adhesins:** Facilitate adhesion to surfaces and host cells.
2. **Invasins:** Enable entry into the tissues of the host.
3. **Proteases:** Degrade tissues and proteins from the host.
4. **Phospholipases:** Cause membrane damage to host cells.
5. **Biofilm formation:** Enables surface colonization and durability.
6. **Morphogenesis:** The transition between the hyphal and yeast forms.
7. **Phenotypic switching:** Modifies surface antigens to elude defensive reactions from the host.
8. **Secreted Aspartic Proteases (SAPs):** Degrade proteins from the host and stimulate lymphocytes.
9. **Lipases:** Degrade lipids in the host.

- 10. Toxic metabolites:** Generate dangerous substances such as acetaldehyde.
- 11. Immune evasion:** Steers clear of the host immune cells' detection.
- 12. Components of the cell wall:** Chitin, beta-glucans, and mannans all enhance pathogenicity.
- 13. Virulence genes:** Control how virulence factors are expressed.
- 14. Quorum sensing:** Controls the expression of virulence factors and the production of biofilms.
- 15. Thigmotropism:** *C. albicans* has the ability to perceive and react to environmental physical characteristics, such as surface topography. This capability facilitates tissue invasion by enabling the fungus to efficiently infiltrate host tissues.
- 16. Stress responses:** Adjust to the conditions of the host and the antifungal medications.

Because of these virulence characteristics, *Candida albicans* is an effective opportunistic pathogen that may colonize, invade, and survive in host tissues. Because of its virulence characteristics, *Candida* actively contributes to the pathophysiology of infection onset and progression. An infection begins when colonization occurs, which is caused by one set of virulence factors, and spreads with the aid of another group [20].

Flexibility in transitioning between several morphogenic stages

The variety of cellular development states that *Candida albicans* exhibits aids in its establishment and persistence in many mammalian tissues. Different filamentous or yeast-like morphologies, colony characteristics, and unique genetic profiles are linked to these cell phenotypic variances [21]. The capacity of *Candida albicans* to transform its shape between the yeast and hyphal forms is particularly significant in its pathogenic life cycle, as it allows the fungus to penetrate mucosal barriers and cause invasive illness. Yeast, commonly regarded as the commensal form, has the ability to colonize superficial commensal habitats [22, 23]. On the other hand, the hyphal form is generally considered to be the invasive form of the fungus, which permits *Candida albicans* to pierce host barriers and enter deeply seated tissues [24]. The morphological state of *Candida albicans* is influenced by many environmental stimuli, such as pH, host temperature, food availability, and quorum sensing mechanisms [25-28]. It is noteworthy that several anatomical regions in the mouse gut contain distinct hyphal morphotypes and *C. albicans* yeast [29].

The fact that nonfilamentous *C. albicans* strains are avirulent illustrates the significance of the morphogenic shift from yeast to hyphae [30]. The tissue's capacity to manage infection is correlated with *C. albicans*' *in vivo* filament production during systemic candidiasis in mice. As a result, during systemic candidiasis, *C. albicans* forms filaments in the mouse kidney, but neither the liver nor the spleen exhibit filamentation. This tissue-specific propensity to filament is associated with the liver's and spleen's ability to control the infection, in contrast to the kidney, which is unable to control fungal proliferation and gradually loses function [31].

Adhesion, invasion, and host cell damage

The variety of surfaces that *Candida albicans* can colonize, from host mucosal tissues to medical devices and tools,

emphasizes the significance of adhesion and invasion elements for the pathogen's ability to succeed. The yeast cells of *Candida albicans* attach themselves to the epithelium and/or endothelium in tissue, causing hyphal extension and subsequent active host cell penetration. Members of the Als and Hwp1 families' adhesin and invasin mediate the process [32-34].

Fungal ligands interact with epithelial cells during mucosal infection, causing induced endocytosis and active penetration by *Candida albicans*. Active penetration during systemic infection can open blood arteries, allowing fungal cells to travel to distant body locations. After then, colonization and the spread of illness are started by endothelium penetration [35]. The adhesins and invasins Als3 and Ssa1 bind host cell N-cadherin on endothelial cells and E-cadherin on oral epithelial cells, thereby mediating induced endocytosis [36]. Developmentally down-regulated protein 9 (NEDD9) signaling and platelet-derived growth factor BB (PDGF BB) are activated in oral epithelial cells through induced endocytosis [37]. Hyphae that are formed after *Candida albicans* adheres to epithelial cells are able to aggressively penetrate the plasma membrane of these cells [38, 39]. The expression of hypha-associated proteins, which are known to cause harm and activate the immune system, coincides with the development of hyphae [64].

It has recently been demonstrated that Candidalysin, a recently identified peptide toxin generated from hyphae, is a key factor in *Candida albicans* pathogenicity. The Ece1p protein is encoded by ECE1, which is expressed by hyphal filaments. Kex2p and Kex1p metabolize Ece1p to produce mature candidalysin, which is subsequently secreted. High quantities of candidalysin cause membrane degradation by interacting with cell membranes to produce pore-like structures [41, 42]. Rapid necrotic as opposed to apoptotic cell death is the outcome of the oxidative stress and subsequent calcium influx that are caused in the host cells [43]. Albumin, which functions as an anti-toxin through hydrophobic interactions, neutralizes the toxin, perhaps providing an immunological defense against chronic candidalysin damage [44].

Stress resistance

Differential stress resistance responses must be induced by *Candida albicans* in response to the numerous stresses that it faces from host immune cells and varied cues from its surroundings. For instance, *C. albicans* has six Superoxide Dismutases (SODs) that help detoxify Reactive Oxygen Species (ROS) by converting O_2^- into molecular oxygen and hydrogen peroxide, allowing the fungus to evade oxidative death by immune cells [56]. As a result, *C. albicans* strains lacking Sod had lower pathogenicity [57]. Attenuating oxidative stress is aided by additional fungal antioxidant proteins and DNA damage repair genes [58, 59]. Additional stressors include treatment with antifungal drugs, nitrosative stress, temperature and osmolarity variations, and changes in pH [60, 61, 62]. Heat shock proteins (Hsps), especially Hsp90, regulate a number of the fungal stress responses. Stabilizing various signal transducers is the function of Hsp90, an ATP-dependent molecular chaperone that is widely distributed and conserved. Drug resistance and fungal pathogenicity are made possible by *C. albicans* Hsp90. The stress-activated protein kinase Hog1/Sty1, the mitogen-activated kinase Mck1, and/or the protein phosphatase calcineurin are all modulated to produce this effect [63].

Immune evasion by masking cell wall components

The identification of fungal Pathogen-Associated Molecular Patterns (PAMPs) by host epithelial and immune cell Pattern Recognition Receptors (PRRs) is the initial stage in the formation of an immunological response to *Candida albicans*. Chitin, β -glucan, and mannoproteins make up the cell wall of *Candida albicans*. These substances are identified by PRRs on host cells and are crucial for triggering protective antifungal immune responses. By concealing cell wall components in response to metabolic signals, *Candida albicans* cells can decrease their exposure to PAMP and prevent immunological pathways that initiate these effector responses. By taking advantage of host signals, these defensive reactions work around the immune system to encourage immune evasion. Changes in the availability of oxygen, the source of carbon, or hormone levels are a few examples of these signals. As with pH or iron changes, environmental stress during infection can also modify the architecture of the fungal cell wall in a way that favors immune detection.

Conclusion

In summary, *Candida albicans* is a potent opportunistic pathogen that seriously jeopardizes human health, especially in those with weakened immune systems. It may colonize, invade, and stay in host tissues thanks to its arsenal of virulence factors, which includes adhesins, invasins, and secreted enzymes. This can result in a variety of clinical presentations, ranging from minor mucosal infections to the potentially fatal invasive candidiasis. Comprehending the intricate relationship between *C. albicans* virulence factors and host immune responses is essential for creating efficient diagnostic, treatment, and prophylactic approaches. In order to identify new targets for antifungal medication and to fully understand the molecular mechanisms underlying the pathogenesis of *Candida albicans*, more study is required. In the end, to address the rising number of *C. albicans* infections and enhance patient outcomes, a thorough strategy integrating basic research, clinical inquiry, and public health campaigns is needed. Because the variables and mechanisms underlying *C. albicans*' pathogenicity are so diverse, including dimorphism, biofilm formation, thigmotaxis, adhesion protein expression, and extracellular hydrolytic enzyme secretion, it is critical to understand them fully. Life-threatening infections ranging from superficial to systemic can be brought on by *Candida albicans*.

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