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Mini Review

Candida Glabrata- Pathogenesis and Therapy

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Abstract

Candida species has been on the rise in recent years. Species Candida glabrata is the second most common candidate for candidiasis and is associated with a high rate mortality in immunocompromised patients. *Candida glabrata* is an increasing cause of candidemia, especially at cancer and bone marrow transplant centers where fluconazole is used for antifungal prophylaxis. This yeast is less susceptible to fluconazole in vitro than is Candida albicans. Pathogenicity infections are most commonly seen in the elderly, immunocompromised, and AIDS patients. It is most importantly known as an agent of urinary tract infections. In fact, 20% of all urinary yeast infections are due to C. *glabrata*, although they may be asymptomatic and left untreated. Patients with invasive infections such as those of blood, bones, heart, urinary tract and the brain are treated with intravenous amphotericin B or flucanozole for 48 to 72 hours until the infection is under control. This is followed by oral administration of the drugs for 2 to 6 weeks for the complete eradication of C. *glabrata* from the patient's body. Recent advances in the C. *glabrata* molecular tool box should aid research into its virulence mechanisms, host–pathogen relationship and reveal novel putative drug targets.

INTRODUCTION

Since 1995, Candida species have become the fourth most common cause of nosocomial bloodstream infection and are associated with a crude mortality rate of 39%, which is the highest mortality rate associated with any cause of nosocomial bloodstream infections [1].

Candidiasis is a type of infection caused by fungi of the genus Candida, most commonly Candida albicans. This microbial is commonly found on the skin, in the digestive and genital tract, the mouth and throat. To infection, i.e. excessive propagation and spread of the fungus occurs when, for certain reasons, the balance between the fungus and the bacterial flora that regulates its propagation is disturbed [2]. Then there is the development of an infection, which can affect the skin, nails, oral cavity and full organs. This disease affects as many as 75% of women, and in 10% of cases it is a permanent problem [3]. The type of Candida albicans is the most common, but not the only candidate for candidiasis whose clinical picture may vary from mild surface infections to life-threatening systemic diseases. Number Infection caused by non-albicans Candida species has been on the rise in recent years. Species Candida glabrata is the second most common candidate for candidiasis and is associated with a high rate mortality in immunocompromised patients [4, 5]

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PATHOGENESIS

Candida glabrata, once known as Torulopsis glabrata, is a common nonhyphae forming yeast isolate in the clinical laboratory. It is a member, along with over 200 other species, of the Candida genus [6]. The fungal cell wall is the predominant site of interaction between the fungus and its host. This cell wall consists of a complex structure of polysaccharides, proteins, and lipids, but its composition is dynamic, responding to changes in the local environment. Expansion of the fungal wall during growth involves permanent remodeling of the cell wall polysaccharide network, which is comprised of three major types of polysaccharide: mannans, β-glucans, and chitin **[7].** Chitin is a homopolymer of β1, 4-N-acetylglucosamine (GlcNAc) and is essential for biological functions in fungi, including cell division, forming the primary septum of all septa, hyphal growth, and virulence. Chitin synthesis in *C. glabrata* is carried out by chitin synthases. Deregulation of chitin biosynthesis is a potential mechanism of virulence and resistance to antifungal treatments [8-11].

Pathogenicity infections are most commonly seen in the elderly, immunocompromised, and AIDS patients. It is most importantly known as an agent of urinary tract infections. In fact, 20% of all urinary yeast infections are due to C. glabrata, although they may be asymptomatic and left untreated [12].

At present, the virulence factors associated with *C. glabrata*, relative to other pathogenic yeast species like C. albicans are poorly understood. When compared with *C. albicans, C. glabrata* can sometimes be considered to be "less virulent".

Furthermore, its inability to secrete proteases led it to originally being called Torulopsis glabrata the species was only reclassified to Candida because of its human Pathogenicity. There is agreement that the two major functional differences between *C. albicans* and *C. glabrata* are the inability of *C. glabrata* to form true hyphae and to secrete certain proteases.

More serious infections would include rare cases of endocarditis, meningitis, and disseminated infections (fungaemias). It has the ability to form sticky "biofilms" that adhere to living and non-living surfaces (such as catheters) thus forming microbial mats, making treatment more difficult. Recently a shift has been noted from fungal disease caused by C. albicans to that of non-albicans species of Candida, such as glabrata, especially in ICU patients [13,14].

This phenomenon is copied by selection less sensitive strains of *C. glabrata* yeast by the wide use of fluconazole as a prophylactic and therapeutics. One of the most important yeast virulence factors for *C. glabrata* is the ability to adhere to tissues host and a biotic surface, and the establishment of a colonization process and the formation of a biofilm [**15].** Biofilms represent a serious clinical problem because they increase resistance to antifungal therapy and protects the cells within the biofilm from the immune response of the host [16].

The pathogenesis of yeast *C. glabrata* is mediated by numerous virulence factors, of which the most important adhesion ability to the tissue of the host and medical devices, the formation of biofilm and secretion of hydrolytic enzymes. Initial adherence to candida is conditioned by non-specific factors (hydrophobic and electrostatic forces) and is supported by specific adhesives on the surface of fungal cells that recognize ligands such as proteins, fibrinogen, and fibronectin [17]**.**

The amount of fungal adhesion may also depend on the surface properties of the microorganism and a biotic surfaces, such as hydrophobicity, zeta potentials and surface roughness. Surface roughness is in a positive correlation with the rate of fungal colonization of biomaterials, so that uneven surface may be a risk factor for adhesion to microorganisms and formation biofilm [18]**.**

The formation of biofilms carries important clinical features consequences due to increased resistance to antimycotics and cell abilities within biofilms to withstand the immune host system. For many pathogenic fungi, pH is considered an important factor in adhesion to host tissue. Within the human organism of the *C. glabrata* species covers a wide range of pH values from the acidic pH in stomach and vagina through neutral and slightly basal in the bloodstream and many organs. The ability to grow at temperatures typical of human fever (37-39**°C**) is a very important feature of pathogen virulence [19]**.**

Adaptation could be attributed to C. glabrata's ability to adhere to a variety of surfaces from host tissue to medical devices. *C. glabrata* is one of the most robust Candida species and can survive on inanimate surfaces for five months, while C. albicans cannot survive beyond four months [20]**.** Rodrigues et al. [21]**,** note that this adaptation has most likely arisen from *C. glabrata's* response to stresses like oxidative stress, nutrient limitation, competition with other microorganisms and the lack of sporulation. Fidel et al. [22]**,** Note that *C. glabrata* is not as sensitive to environmental conditions as C. albicans despite both species having comparable cell surface hydrophobicity properties. However, in a more recent study it was found that *C. glabrata* has a notably higher relative cell-surface hydrophobicity than other Candida species [23]**.**

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THERAPY

Resistance to antifungal treatment by *C. glabrata* was almost unheard of prior to HIV infection. However, with growing numbers of patients being unable to rid invasive candidiasis due to compromised immune systems and/or increased widespread antifungal usage, the drug resistance phenomenon is of immense concern to the medical community. The proportion of azole resistance in clinical isolates across several countries has been shown to increase in the period from 2001 to 2007. In C. glabrata, several mechanisms of azole resistance have been identified: increased P-450-dependent ergosterol synthesis and an energy-dependent efflux pump of fluconazole, possibly via a multidrug resistance-type transporter [25]**.** Moreover, a study by Pfaller et al. showed resistances to echinocandins of fluconazole-resistant *C. glabrata* isolates was shown to have increased from no cases between 2001 and 2004 to a 9.3% frequency in the time period of 2006–2010 supporting the notion that drug resistance in *C. glabrata* is rapidly developing [**26].**

Recently, it was determined that phenotype switching does occur in *C. glabrata* [27]**.** It is interesting that such a phenomenon would occur in nondimorphic organisms as well as in haploid organisms. Although the relationship of this *C. glabrata* phenotype switching to virulence is unknown, it may enhance virulence and play a role in causing symptomatic infection.

Polyene antifungals such as amphotericin B, nystatin and primaricin kill fungal organisms by interacting with ergosterol in the cell membrane. This, in turn, creates channels within the cell membrane causing small molecules to leak, resulting in cell death.

Patients with invasive infections such as those of blood, bones, heart, urinary tract and the brain are treated with intravenous

amphotericin B or flucanozole for 48 to 72 hours until the infection is under control. This is followed by oral administration of the drugs for 2 to 6 weeks for the complete eradication of *C. glabrata* from the patient's body. However, according to the John Hopkins Point of Care Information Technology Center, strains of *C. glabrata* exhibit significant resistance to flucanozole and other azole drugs. Patients being treated with these drugs should be continuously monitored for treatment response. Amphotericin B, on the other hand, can cause severe side effects, especially when given intravenously. Caspofungin is another antifungal that can be used, although its efficacy to treat invasive infections has not been well studied [28, 29].

The more recently introduced antifungals, echinocandins, include capsofungin, micofungin and anidulafungin, and are a typical first line therapy for invasive candidiasis [30, 31].

CONCLUSION

Recent advances in the *C. glabrata* molecular tool box should aid research into its virulence mechanisms, host–pathogen relationship and reveal novel putative drug targets. Thanks to the partial *C. glabrata* deletion collection, high-throughput screening aimed at elucidating novel drug targets can now take place alongside screens for genes involved in virulence by utilizing one of the new virulence models for preliminary screens before moving to the classical mouse model for further corroboration.

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