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Review Article

Mechanisms of Adaptation Pathogenicity and Resistance in *Candida glabrata*

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Abstract

Candida glabrata has emerged as a significant opportunistic fungal pathogen, ranking as the second most common cause of candidiasis globally. Its increasing prevalence is attributed to the rise in immunocompromised populations, frequent use of indwelling medical devices, and its ability to develop resistance to antifungal drugs. C. glabrata exhibits unique adaptation strategies, including genetic diversity and plasticity, metabolic flexibility, stress response mechanisms, and biofilm formation. Its pathogenicity is characterised by adhesion factors, invasion strategies, evasion of host immune responses, and virulence factors. Notably, C. glabrata exhibits high intrinsic resistance to antifungal drugs, particularly azoles, and can rapidly acquire resistance to multiple classes of drugs. The molecular basis of drug resistance involves efflux pumps, targ*et al*terations, and mutator phenotypes caused by mismatch repair defects. Biofilm-associated resistance contributes to persistence and low therapeutic response. Diagnosing C. glabrata infections presents challenges due to its ability to evade host immune responses and the limitations of phenotypic susceptibility testing. Current treatment strategies involve antifungal therapies, combination therapies, and exploration of novel therapeutic targets. Understanding the complex interplay among C. glabrata virulence mechanisms, drug resistance, and host immune responses is crucial for developing effective management strategies and combating this emerging pathogen.

Keywords: *Antifungal Resistance; Biofilm Formation; Candida glabrata; Stress Adaptation; Virulence Factors*

Introduction

Overview of Candida glabrata as an opportunistic fungal pathogen

Candida glabrata has risen to prominence as a significant opportunistic fungal pathogen, becoming the second most common cause of candidiasis, with infections ranging from superficial to potentially fatal systemic diseases (Kumar *et al*., 2019; Schwarzmuller *et al*., 2014). Despite its name, *C. glabrata* is more closely related evolutionarily to the non-pathogenic yeast Saccharomyces cerevisiae than to other Candida species like *C. albicans (*Figure-1). This haploid budding yeast, which primarily reproduces asexually, has become a major health concern due to its increasing prevalence over the last two decades (Kumar *et al.,* 2019; Carreté *et al.,* 2019). Interestingly, *C. glabrata* lacks the typical virulence factors found in other Candida species, such as morphological switching and secreted proteolytic activity (Rasheed, Battu & Kaur, 2020). However, it possesses unique characteristics that contribute to its pathogenicity, including cell surface-associated adhesins, biofilm formation, stress response mechanisms, and the ability to survive and multiply within macrophages (Kumar *et al*., 2019; Kasper, Seider & Hube, 2015). Moreover, *C. glabrata* demonstrates high intrinsic resistance to various

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antifungal drugs, especially azoles, making it a challenging pathogen to treat clinically (Frías-De-León *et al*., 2021).

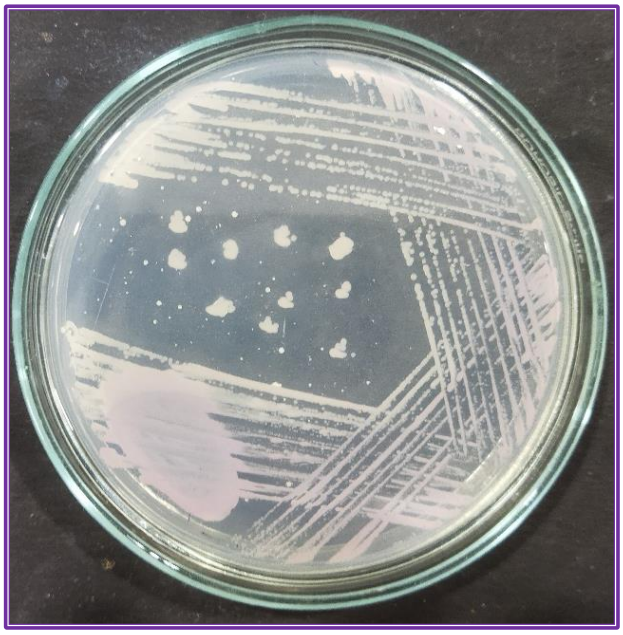

Figure 1: Representative colony morphology of Candida glabrata isolated from clinical specimens of head and neck origin, including oral cavity and throat swabs. Colonies were cultured on selective CHROMagar medium, displaying characteristic smooth, cream-to-pale pink colonies after 48 hours of incubation at 30°C

Increasing clinical importance and prevalence

The increasing clinical importance of *C. glabrata* is attributed to several factors, including an increase in immunocompromised populations, such as patients with AIDS, cancer, and diabetes, as well as the growing elderly population and frequent use of indwelling medical devices (Hassan, Chew & Than, 2021). The prevalence of *C. glabrata* has also been linked to its ability to develop resistance to antifungal drugs, particularly azoles such as fluconazole (Gamal *et al.,* 2021; Whaley & Rogers, 2016). Although *C. gglabrata* is generally considered a high-priority pathogen, its prevalence varies significantly among countries (Arastehfar *et al*., 2023). Additionally, *C. glabrata* can form "petite" colonies with attenuated growth rates, which has led to controversies regarding their clinical importance. However, these petite cells can become dormant when engulfed by macrophages, potentially evading antifungal treatments (Arastehfar *et al*., 2023).

Comparison with other Candida species

Candida glabrata is one of the most common non-albicans Candida species that cause fungal infections, particularly in immunocompromised patients. Compared to other Candida species, *C. glabrata* has some distinct characteristics: it is generally less susceptible to azole antifungals, particularly fluconazole, than *C. albicans*, and studies have reported reduced susceptibility rates of 40.6% and 37.2% to fluconazole and posaconazole, respectively (Schmalreck *et al*., 2012) Table-1. This reduced azole susceptibility is a key factor contributing to the increasing incidence of C. glabrata infections (Turner & Butler, 2014). Interestingly, *C. glabrata* infections are associated with older age and chronic diseases, in contrast to *C. tropicalis*, which is more common in younger patients with severe neutropenia or acute leukaemia (Weinberger *et al*., 2005). Additionally, *C. glabrata* has shown higher biofilm-forming ability than *C. albicans, C. tropicalis, and C. krusei* in single-species biofilms (Rodrigues, Silva & Henriques, 2014).

Table 1: Comparison of Candida glabrata with Other Candida Species

Feature	*Candida glabrata*	*Candida albicans*	*Candida tropicalis*	*Candida krusei*	References
Prevalence	Common in immunocompromised patients, particularly older individuals with chronic diseases.	Most common Candida species causing infections.	More common in younger patients with neutropenia or acute leukemia.	Less common but causes infections in immunocompromised individuals.	Turner and Butler *et al*., 2014
Azole Susceptibility	Reduced susceptibility to fluconazole (40.6%) and posaconazole (37.2%).	Generally susceptible to azoles but resistance is increasing.	Variable susceptibility; resistance is less common than in *C. glabrata* .	Intrinsically resistant to fluconazole.	Schmalreck *et al*., 2012; Turner and Butler *et al*., 2014
Biofilm Formation	High biofilm-forming ability compared to C. albicans, *C. tropicalis*, and *C. krusei.*	Moderate biofilm-forming ability.	Moderate biofilm-forming ability.	Lower biofilm-forming ability than *C. glabrata*.	Rodrigues, Silva & Henriques, 2014
Virulence Factors	Lacks typical hyphae formation but produces biofilms and secretes enzymes.	Produces hyphae, biofilms, and secretes hydrolytic enzymes (proteases, lipases).	Produces biofilms, proteases, and lipases.	Limited enzyme production and low virulence compared to other species.	Rodrigues, Silva & Henriques, 2014
Association with Host	Frequently associated with systemic infections and invasive candidiasis.	Commonly causes mucosal infections (oral, vaginal) and systemic infections.	Frequently found in bloodstream infections in neutropenic patients.	Primarily causes invasive candidiasis in immunocompromised patients.	Turner and Butler *et al*., 2014; Weinberger M *et al*.,2005
Patient Demographics	Older adults with comorbidities (diabetes, cancer, etc.).	Broad demographic, including immunocompromised and healthy individuals.	Younger patients with haematological malignancies.	Cancer patients and those on long-term antifungal therapy.	Weinberger M *et al*.,2005

Adaptation

Genetic Diversity and Plasticity

Candida glabrata demonstrates exceptional genetic variability and adaptability, which are essential for its survival in diverse environments, including human hosts. The genome of *C. glabrata* is highly flexible, capable of enduring a broad spectrum of modifications in response to changing conditions (Mba *et al*., 2022). This genomic adaptability enables the pathogen to swiftly adjust during infections and develop resistance to antifungal therapies. Research has uncovered significant genetic variations within clonally infecting populations of *C. glabrata*, and analyses of sequential clinical isolates from individual patients have revealed an enrichment of non-synonymous alterations in genes encoding cell wall proteins, indicating an ongoing selection process within the host (Carreté *et al*., 2019). Moreover, copy number variations and other genomic modifications accumulate during infection, potentially underlying phenotypic differences in traits relevant to pathogenicity (Carreté *et al*., 2019). Notably, *C. glabrata* utilises various strategies to generate its genetic diversity. More than half of *C. glabrata* clinical isolates harbour mutations in the DNA mismatch repair gene MSH2, resulting in a mutator phenotype that increases the frequency of drug-resistant mutants (Healey *et al*., 2016). Furthermore, extensive chromosomal rearrangements have been observed among *C. glabrata* strains, leading to numerous distinct karyotypes within the species that can occur during antifungal treatment, as documented in sequential isolates from individual patients (Healey *et al*., 2016).

Metabolic flexibility and nutrient acquisition strategies

Candida glabrata exhibits remarkable metabolic flexibility and nutrient acquisition strategies, which contribute to its pathogenicity and ability to survive in diverse host environments. The glyoxylate cycle plays a crucial role in the alternative carbon metabolism of *C. glabrata*, allowing the utilisation of non-fermentable carbon sources when glucose is limited (Chew, Chee & Than, 2019). This metabolic adaptation is particularly important for survival within nutrient-poor host niches such as macrophage phagosomes (Seider *et al*., 2014; Vincent *et al*., 2016). Interestingly, the *C. glabrata* genome lacks some evolutionary ancient metabolic pathways that are present in other fungal pathogens, indicating a unique evolutionary trajectory (Nene *et al*., 2021). Despite these gaps, *C. glabrata* has developed efficient nutrient acquisition mechanisms, particularly for iron uptake, which is crucial for intraphagosomal survival (Seider *et al*., 2014). The ability to adapt to nutrient-limited conditions and different carbon sources is regulated by complex networks that link metabolism, stress adaptation, and cell wall remodelling (Brown *et al*., 2014).

Stress response mechanisms (oxidative, osmotic, thermal)

Candida glabrata possesses exceptional stress-response mechanisms, particularly in relation to oxidative stress, enabling it to endure higher levels of H_2O_2 compared to *Saccharomyces cerevisiae* and Candida albicans (Cuéllar-Cruz *et al*., 2008). This enhanced resistance to oxidative stress is a crucial virulence characteristic that enables C. glabrata to persist in mammalian hosts and avoid destruction by the immune system (Gutiérrez- Escobedo *et al*., 2020; Roetzer, Gabaldón & Schüller, 2011). The oxidative stress response in *C. glabrata* involves several key components. The transcription factors Yap1p, Skn7p, and Msn4p work together to provide stationary-phase cell resistance to oxidative stress. Furthermore, the sulfiredoxin Srx1 and peroxiredoxins Tsa1 and Tsa2 have been shown to play a role in the oxidative stress response and are essential for virulence (Gutiérrez- Escobedo *et al*., 2020). Notably, while Tsa1 is expressed constitutively, Srx1 and Tsa2 are induced in the presence of H_2O_2 and depend on both the Yap1 and Skn7 transcription factors (Gutiérrez- Escobedo *et al*., 2020). The stress response mechanisms of C. glabrata significantly contribute to its pathogenicity and drug resistance. The fungus's ability to withstand oxidative stress allows it to survive within phagocytic cells, such as neutrophils (Gutiérrez- Escobedo *et al*., 2020). Additionally, the extensive genetic diversity and genome plasticity of C. glabrata enable it to adapt to various stressors, including antifungal drugs (Healey *et al*., 2016). In combination with its stress resistance mechanisms, *C. glabrata* emerges as a formidable pathogen capable of persisting during antifungal treatment and developing multidrug resistance (Lee, Robbins & Cowen, 2023; Lewis, Viale & Kontoyiannis, 2012) (Table 2).

Table 2: Comparative Stress-Response Mechanisms of Candida glabrata, Candida albicans, and Saccharomyces cerevisiae

Stress Type	**Stress-Response Mechanisms**	***Candida glabrata***	***Candida albicans***	**Saccharomyces cerevisiae**	**References**
Oxidative Stress	Ability to withstand H_2O_2	Exhibits higher resistance; key players: Yap1p, Skn7p, Msn4p, Srx1, Tsa1, Tsa2	Moderate resistance; Yap1 and Cap1 involved in detoxifying ROS	Lower resistance compared to C. glabrata; Yap1 transcription factor plays a central role	Cuéllar *et al*.,2008; Gutiérrez-Escobedo *et al*., 2020; Roetzer, Gabaldón, & Schüller, 2011
	Role in survival and immune evasion	Survives oxidative bursts within phagocytes like neutrophils	Produces catalase and superoxide dismutase for ROS detoxification	Primarily uses catalase and glutathione pathways for oxidative stress	Gutiérrez-Escobedo *et al*., 2020; Healey *et al*.,2016; Lewis, Viale & Kontoyiannis, 2012
	Gene expression under oxidative stress	Srx1 and Tsa2 are H_2O_2-induced; Tsa1 is constitutively expressed	Catalase and glutathione reductase gene expression upregulated	Similar to C. albicans but less effective	Gutiérrez-Escobedo *et al*.,2020; Tscherner *et al*.,2011

Thermal Stress	Adaptation to temperature fluctuations	Tolerance to high temperatures (37–42°C)	Optimal growth at 37°C but exhibits thermotolerance during infection	Moderate thermal stress tolerance (up to 37°C)	Lee, Robbins & Cowen, 2023; Healey *et al*.,2016
	Mechanisms employed	Induction of heat-shock proteins (Hsps); major chaperones include Hsp104 and Ssa proteins	Hsp90 and Hsp70 chaperones regulate protein folding under thermal stress	Uses Hsp104 and Ssa proteins for thermal tolerance	Lewis Lewis, Viale & Kontoyiannis 2012; Roetzer, Gabaldón, & Schüller, 2010
Osmotic Stress	Response to hyperosmolarity	Enhanced osmotic stress resistance through activation of the HOG pathway	Moderate osmotic stress resistance; HOG1 pathway activation required	Similar to C. albicans; less osmoadaptive in hyperosmotic environments	Healey *et al* .,2016; Tscherner *et al*.,2011
	Pathways involved	HOG (high osmolarity glycerol) pathway; glycerol production via GPD1 upregulated	Glycerol accumulation via the HOG pathway	HOG pathway activation for glycerol synthesis	Cuéllar *et al*.,2008; Roetzer, Gabaldón & Schüller, 2011; Lee, Robbins & Cowen, 2023
Drug Resistance	Adaptation to antifungal stress	Genome plasticity enables rapid resistance development; efflux pumps (Cdr1, Cdr2)	Relies on efflux pumps and biofilm formation	Moderate resistance; less genome plasticity compared to Candida spp.	Healey *et al* .,2016; Tscherner *et al*.,2011; Lewis, Viale & Kontoyiannis , 2012
Genome Adaptability	Genetic plasticity and mutation rates	Extensive genome plasticity allows rapid adaptation to stressors, including antifungals	Moderate genetic adaptability; biofilm-associated resistance mechanisms	Limited genetic diversity compared to C. glabrata	Healey *et al*.,2016; Gutiérrez-Escobedo *et al*.,2020
Immune Evasion	Ability to evade immune system	Survives within neutrophils and macrophages; resists phagocytic killing	Produces hyphal structures and secretes enzymes to evade immune responses	Limited immune evasion mechanisms; primarily uses antioxidant defences	Gutiérrez-Escobedo *et al*.,2020; Lewis, Viale & Kontoyiannis, 2012; Cuéllar *et al*., 2008

Biofilm formation and its role in adaptation

Biofilm formation is a crucial virulence factor in *C. glabrata* that contributes to its pathogenicity and survival in the host environment (Rodrigues, Silva & Henriques, 2014; Timmermans *et al*., 2011). Biofilm formation allows *C. glabrata* to adhere strongly to various substrates, including medical devices, which is facilitated by the expression of numerous adhesin-encoding genes. These adhesins play vital roles in the initial stages of infection and subsequent biofilm development. Interestingly, the number of adhesin-encoding genes in *C. glabrata* correlates with its pathogenicity compared with closely related species (Timmermans *et al*., 2011).*C. glabrata* biofilms exhibit high tolerance to antifungal treatments, making them challenging to eradicate (Alves, Precioso & Becoña, 2021).This resistance is attributed to the complex structure of the biofilm matrix and the various molecular mechanisms (Rodrigues, Silva & Henriques, 2014).Recent studies have identified key genes and pathways involved in biofilm formation and antifungal resistance, including Yak1 kinase and the Swi/Snf chromatin remodelling complex, which regulate the expression of adhesin-encoding genesEPA6 and EPA7(d'Enfert *et al.,* 2021). Additionally, the multidrug resistance transporter, CgTpo1_2, plays a role in biofilm formation and virulence (Santos *et al*.,2017).

Pathogenicity

Adhesion factors and host cell interaction

A crucial virulence mechanism is the capacity to strongly attach to various substrates, and genomic analyses have shown a link between pathogenicity and the number of genes encoding adhesions (Timmermans *et al*., 2018). Research has demonstrated that the EPA1 gene, which encodes a lectin-like adhesin, is responsible for 95% of C. glabrata's adherence to human epithelial cells (Cormack, Ghori, & Falkow, 1999). Notably, C. glabrata lacks the ability to transition to filamentous growth, a key virulence trait in C. albicans. However, it has evolved alternative mechanisms to enhance its pathogenicity (Kumar *et al*., 2019; Tscherner, Schwarzmüller & Kuchler*,* 2011). These include the synthesis of proteases, phospholipases, and haemolysins, as well as the creation of biofilms that enable the complex to evade host immune responses and develop fungal resistance. Furthermore, C. glabrata exhibits a remarkable ability to endure and thrive within host immune cells, further contributing to its pathogenic nature (Kumar *et al*., 2019; Tscherner, Schwarzmüller & Kuchler*,* 2011).

Invasion strategies and tissue damage

Candida glabrata employs various strategies for invasion and tissue damage, despite the lack of virulence factors found in other Candida species. Unlike *C. albicans*, *C. glabrata* are unable to form filaments, which are typically associated with tissue invasion. However, it possesses a large repertoire of adhesins that facilitate adherence to the host epithelium, contributing to its pathogenicity (Tscherner, Schwarzmüller & Kuchler*,* 2011). Interestingly, *C. glabrata* causes surprisingly low damage and cytokine release when interacting with macrophages, which are key components of the innate immune system (Kasper Seider & Hube, 2015). This pathogen has evolved mechanisms to survive and replicate inside macrophages, including poor host cell activation, modification of phagosome maturation and pH, adaptation to antimicrobial activities, and overcoming nutrient limitations within phagosomes (Kasper Seider & Hube, 2015). This intracellular survival strategy may serve as a mechanism for immune evasion and persistence during infection (Kasper Seider & Hube, 2015; Kumar *et al*., 2019).

Evasion of host immune responses

Candida glabrata utilises numerous tactics to circumvent host immune defences, enhancing its pathogenicity. This fungus can endure and multiply within host immune cells, especially macrophages, which serve as the initial barrier against invading pathogens (Kumar *et al*., 2019; Tscherner, Schwarzmüller & Kuchler*,* 2011). A crucial aspect of *C. glabrata's* immune evasion strategy is its capacity to thrive and reproduce inside macrophages while inducing minimal harm and cytokine production (Kasper Seider & Hube, 2015). Notably, CgPDR1 gain-of-function mutations, linked to azole resistance, also result in reduced adherence to and uptake by macrophages. This may enable C. glabrata to dodge the host's innate cellular immune response (Vale-Silva *et al*., 2013). However, these mutations enhance adherence to epithelial cells, potentially promoting host colonisation (Vale-Silva *et al*., 2013). C. glabrata's immune evasion mechanisms involve altering phagosome maturation and pH, adjusting to antimicrobial activities, and overcoming nutrient scarcity within phagosomes (Kasper Seider & Hube, 2015). The fungus can suppress the host inflammatory immune response (Kumar *et al*., 2019). These adaptations, combined with their ability to form biofilms and high inherent resistance to antifungal drugs, contribute to *C. glabrata's* success as an opportunistic pathogen (Cavalheiro & Teixeira, 2018; Tscherner, Schwarzmüller & Kuchler*,* 2011). Comprehending these evasion strategies is essential for developing effective treatments against *C. glabrata* infections.

Virulence factors and their regulation

Candida glabrata possesses several factors that contribute to its pathogenicity, including adherence to host surfaces, production of hydrolytic enzymes, biofilm formation, and stress resistance mechanisms (Hassan, Chew & Than, 2021). The fungus has a large repertoire of adhesins involved in adherence to the host epithelia, which is crucial for infection initiation (Tscherner, Schwarzmüller & Kuchler*,* 2011). *C. glabrata* also produces proteases, phospholipases, and haemolysin, which aid in evading the host immune response (Frías-De-León *et al*., 2021). Unlike *Candida albicans*, *C. glabrata* lacks the ability to switch to filamentous growth, which is considered a major virulence trait. However, *C. glabrata*

compensates for this with other virulence mechanisms, such as its remarkable ability to persist and survive inside the host immune cells (Tscherner, Schwarzmüller & Kuchler, 2011). The regulation of virulence factors in *C. glabrata* involves several transcription factors, including Yap1p, Skn7p, and Msn4p, which play crucial roles in the stress response and adaptation (Cuéllar-Cruz *et al*., 2008; Roetzer, Gabaldón & Schüller, 2011).

Resistance Mechanisms

Antifungal drug resistance (azoles, echinocandins, amphotericin B)

Candida glabrata has become a significant health concern due to its rapid development of resistance to multiple classes of antifungal drugs, including azoles and echinocandins (Healey *et al*., 2016). The resistance mechanisms in *C. glabrata* are predominantly acquired rather than innate, involving various cellular and genetic adaptations. This organism uses multiple strategies for azole resistance, such as activating efflux systems, decreasing drug uptake, altering the target site, increasing target enzyme production, and developing alternative pathways (Pukkila-Worley *et al.,* 2009). Specifically, azole resistance is linked to the overexpression of efflux pumps (CDR1 and CDR2) and mutations in the ergosterol biosynthesis pathway (ERG11) (Czajka *et al*., 2023). Resistance to echinocandins in *C. glabrata* is associated with point mutations and/or overexpression of FKS1 and FKS2, which play a role in cell wall synthesis (Czajka *et al*., 2023; Pemán, Cantón & Espinel-Ingroff, 2009). Amphotericin B resistance may be facilitated by enhanced catalase activity or deficiencies in ergosterol biosynthesis. Notably, *C. glabrata* exhibits a mutator phenotype resulting from a mismatch repair defect common in clinical isolates. Strains with alterations in the mismatch repair gene MSH2 demonstrate a higher likelihood of breakthrough antifungal treatment both in vitro and in vivo (Healey *et al*., 2016). This genetic mechanism promotes resistance to multiple antifungal agents, partially explaining the high rates of triazole and multidrug resistance associated with C. Glabrata (Arendrup & Patterson, 2017; Healey *et al*., 2016).

Molecular basis of drug resistance (efflux pumps, target alterations)

In C. glabrata, drug resistance at the molecular level involves various mechanisms, with efflux pumps and target modifications playing key roles. Efflux pumps, part of the ABC transporter and major facilitator superfamily, are a primary mechanism of antifungal drug resistance in *C. Glabrata (*Morschhäuser, 2009*)*. These pumps provide resistance to numerous structurally and functionally diverse toxic compounds by actively expelling them from cells. The energy-dependent expulsion of fluconazole, potentially through a multidrug resistance-type transporter, has been identified as a resistance mechanism in C. Glabrata (Parkinson, Hitchcock & Falconer, 1995). Azole resistance is promoted by the overexpression of efflux pump genes such as CDR1, CDR2, and PDR16 (Czajka *et al*., 2023). Target modifications represent another significant resistance mechanism in C. glabrata. Azole resistance can result from mutations in ERG11, which encodes the target enzyme of azoles, and its transcriptional regulator UPC2 (Czajka *et al*., 2023). The primary mechanisms of echinocandin resistance involve point mutations and overexpression of FKS1 and FKS2, which are involved in cell wall biosynthesis (Czajka *et al*., 2023; Pemán, Cantón & Espinel-Ingroff, 2009). Notably, C. glabrata has a higher tendency to develop resistance due to a mutator phenotype caused by mismatch repair defects. Strains with alterations in the mismatch repair gene MSH2 show an increased likelihood of breakthrough antifungal treatment, both in vitro and in mouse models (Healey *et al*., 2016). This genetic mechanism facilitates the acquisition of resistance to multiple antifungals, partially explaining the elevated rates of triazole and multidrug resistance in *C. glabrata*.

Multidrug resistance and cross-resistance patterns

Candida glabrata demonstrates various antifungal resistance mechanisms, with significant concerns regarding multidrug resistance and cross-resistance patterns. The primary mechanism underlying fluconazole resistance in *C. glabrata* has been identified as energy-dependent drug efflux, potentially through a multidrug resistance-type transporter (Parkinson, Hitchcock & Falconer, 1995). This efflux mechanism can result in cross-resistance to other azoles, including ketoconazole and itraconazole.

Moreover, the most common mechanism of azole resistance in *C. glabrata* is the overexpression of multidrug transporters due to activating mutations in PDR1 (Whaley & Rogers, 2016). Notably, C. glabrata has demonstrated the capacity to develop resistance to multiple drug classes, including triazoles and echinocandins. A mutator phenotype, caused by a mismatch repair defect in MSH2, facilitates the acquisition of resistance to various antifungal agents (Rodrigues, Silva & Henriques, 2014). This genetic mechanism partially accounts for the high rates of triazole and multi-drug resistance associated with *C. glabrata*. Furthermore, the emergence of isolates with acquired resistance to both azoles and echinocandins is a major concern, given the limited alternative treatment options (Vale-Silva *et al*., 2013).

Biofilm-associated Resistance

Candida glabrata demonstrates substantial resistance associated with biofilm formation, which plays a crucial role in its pathogenicity (Seneviratne, Jin & Samaranayake, 2008). The biofilm matrix serves as a physical barrier, trapping antifungal drugs and preventing their penetration, thus conferring high resistance to antifungal agents (Borghi, Borgo & Morace, 2016; Dominguez *et al*., 2019). This mechanism is shared among Candida species, including *C. glabrata*, whose matrix is abundant in mannan-glucan polysaccharides (Dominguez *et al*., 2019). Notably, biofilm formation in *C. glabrata* is not only linked to drug resistance but also to increased virulence. The expression of adhesin genes, especially Epa3, has been associated with both biofilm development and reduced intracellular accumulation of azole antifungals (Cavalheiro & Teixeira, 2018). The multifaceted nature of biofilm-associated resistance underscores the intricate relationship between virulence factors and drug resistance mechanisms in Candida glabrata.

Host–pathogen Interactions

Recognition by host immune system

The pathogenicity of C. glabrata is attributed to various factors, including adhesins for host cell attachment, biofilm formation, and stress response mechanisms (Kumar *et al*., 2019). Interestingly, gain-of-function mutations in the CgPDR1 gene not only lead to azole resistance but also enhance virulence. These mutations decrease adherence to and uptake by macrophages, potentially allowing *C. glabrata* to evade innate immune responses. Conversely, they increase adherence to epithelial cells, possibly promoting host colonisation (Vale-Silva *et al*., 2013). The fungus can also disarm macrophages, dampen inflammatory responses, and replicate intracellularly despite lacking morphological switching and secreted proteolytic activity (Kumar *et al*., 2019). In terms of host immune recognition, Dectin-2 plays a crucial role in defence against *C. glabrata*. Dectin-2-deficient mice show increased susceptibility to infection with impaired fungal clearance in the kidneys and reduced production of Th1- and Th17-derived cytokines (Ifrim *et al*., 2014). The ability of *C. glabrata* to persist inside host immune cells and its remarkable genomic plasticity further contribute to pathogenicity and drug resistance (Tscherner, Schwarzmüller & Kuchler*,* 2011). Understanding these complex host-pathogen interactions is critical to creating effective therapeutic strategies against this increasingly important fungal pathogen.

Innate and adaptive immune responses

In contrast to C. albicans, C. glabrata does not exhibit morphological switching and produces proteins with proteolytic activity. Nevertheless, these organisms can successfully evade host immune responses and multiply within cells (Kumar *et al*., 2019; Tscherner, Schwarzmüller & Kuchler*,* 2011). C. glabrata utilises various virulence factors, including adhesins on the cell surface, aspartyl proteases, biofilm formation, and mechanisms for responding to stress (Kumar *et al*., 2019; Tscherner, Schwarzmüller & Kuchler*,* 2011). Notably, the interaction between C. glabrata and host cells is influenced by gain-of-function mutations in CgPDR1, which confer resistance to azoles and enhance virulence (Vale-Silva *et al*., 2013). These mutations reduce adherence to and uptake by macrophages, potentially enabling evasion from innate cellular immune responses while increasing adherence to epithelial cells, thus promoting host colonisation. A key immune evasion strategy of *C. glabrata* is its ability to survive and replicate within macrophages while causing minimal damage and cytokine release (Kasper Seider &

Hube, 2015). The innate immune response to *C. glabrata* involves pattern recognition receptors such as Dectin-2, which contribute to fungal clearance and cytokine production. However, *C. glabrata* has developed mechanisms to resist recognition and suppress classical antimicrobial responses (Jiménez-López & Lorenz, 2013). Adaptive immune responses, particularly cytokines derived from Th1 and Th17 cells, also play a crucial role in host defence against C. Glabrata (Ifrim *et al*., 2014). The intricate interplay between *C. glabrata's* virulence mechanisms and host immune responses underscores the necessity for additional research to develop effective therapeutic strategies against this pathogen.

Immune evasion strategies

This intracellular persistence allows *C. glabrata* to evade the host's innate cellular immune response and may contribute to its ability to develop multidrug resistance (Lewis, Viale & Kontoyiannis, 2012). *C. glabrata* modifies the phagosome environment to enhance its survival. It inhibits phagosome acidification through a heat-sensitive surface attribute, creating a non-acidified environment that is conducive to fungal multiplication (Seider *et al*., 2014). The pathogen also inhibits the production of reactive oxygen species and only marginally increases pro- and anti-inflammatory cytokine levels, with the exception of GM-CSF (Seider *et al*., 2014). These mechanisms contribute to the ability of *C. glabrata* to persist within macrophages as an immune evasion strategy. *glabrata* immune evasion strategies involve intracellular survival, phagosome modification, and minimal host cell activation. These mechanisms, combined with their ability to adhere to host epithelia and adapt to various stresses, contribute to their pathogenicity and persistence during infections (Tscherner, Schwarzmüller & Kuchler, 2011). Understanding these host-pathogen interactions is important for creating effective therapies against *C. glabrata* infections and combating its increasing prevalence in candidemia cases (Katsipoulaki *et al*., 2024).

Diagnostic Approaches

Traditional and molecular methods for identification

Traditional phenotypic methods for identifying *Candida glabrata* are limited in their ability to distinguish C. glabrata from closely related species (Criseo, Scordino & Romeo, 2015). To overcome these limitations, several molecular methods have been developed for more rapid and specific identification of *C. glabrata*: The T2Candida panel is a novel FDA-approved diagnostic platform that can detect *C. glabrata* directly from whole blood samples in less than 5 hours, using magnetic resonance and molecular diagnostics (Zervou *et al*., 2016). Real-time PCR assays using species-specific primers have also been developed, allowing the sensitive detection of *C. glabrata* DNA (Zhang *et al*., 2016). In addition, a PCR-restriction fragment length polymorphism method targeting the intergenic spacer region of ribosomal DNA has been shown to reliably discriminate *C. glabrata* from other related species (Cornet *et al*., 2011). While molecular methods generally outperform traditional culture-based techniques, one study found that PCR detected *C. glabrata* in 24.4% of clinical specimens, compared to only 37% positivity by culture (Camacho-Cardoso *et al*., 2017). This suggests that molecular methods may have higher sensitivity, but antifungal susceptibility testing often relies on culture-based methods (Dagi *et al*., 2016). In conclusion, although traditional phenotypic methods remain in use, molecular techniques, such as real-time PCR, T2 magnetic resonance, and PCR-RFLP, offer more rapid and specific identification of *C. glabrata*, which helps overcome the limitations of conventional methods for distinguishing *C. glabrata* from closely related species and allows for earlier detection to guide appropriate antifungal therapy.

Rapid diagnostic techniques

Rapid diagnostic techniques for *Candida glabrata* have seen significant advancements recently, offering improved speed and accuracy in detection. The T2Candida panel, approved by the FDA, can identify *C. glabrata* and other Candida species in whole blood samples within 5 h using magnetic resonance and molecular diagnostics (Zervou *et al*., 2016). This method offers substantial improvement over traditional culture-based techniques. Molecular diagnostic approaches, including PCR-based assays and DNA sequencing, have shown promising results in enhancing the sensitivity and speed of

invasive fungal disease diagnosis, including *C. glabrata* infection (Halliday *et al*., 2015). A novel assay platform using allele-specific molecular beacons and DNA melt analysis can rapidly identify FKS mutations associated with echinocandin resistance in *C. glabrata* within 3 h, demonstrating 100% concordance with DNA sequencing results (Zhao *et al*., 2016). Non-molecular methods, such as Fourier transform-infrared micro spectroscopy (FTIRM), have also shown potential for rapid identification of *C. glabrata* and other Candida species, as they can identify species from 10- to 18-hour-old microcolonies with 100% accuracy, offering a time- and cost-effective alternative to conventional methods (Essendoubi *et al*., 2016). Additionally, multiplex PCR assays, such as the Luminex Molecular Diagnostics Candida 7-plex panel, have demonstrated 100% sensitivity and specificity in identifying *C. glabrata* and other Candida species in clinical specimens (Babady, Miranda & Gilhuley*,* 2011).

Challenges in diagnosis

Candida glabrata has become a notable opportunistic pathogen, especially in individuals with weakened immune systems, leading to both surface-level and deep-seated infections (Hassan, Chew & Than, 2021; Rodrigues, Silva & Henriques, 2014). Its ability to cause disease stems from several virulence factors, such as attaching to host surfaces, creating biofilms, and producing hydrolytic enzymes (Hassan, Chew & Than, 2021). Unlike Candida albicans, *C. glabrata* cannot form hyphae but makes up for its absence with a wide array of adhesins that enable strong attachment to various surfaces (Tscherner, Schwarzmüller & Kuchler*,* 2011). A significant obstacle in managing *C. glabrata* infections is their inherent high resistance to antifungal medications, particularly azoles, and their quick development of resistance to multiple drug types (Healey *et al*., 2016; Tscherner, Schwarzmüller & Kuchler*,* 2011). Resistance often develops due to extended antifungal exposure and can involve different mechanisms, including increased expression of drug efflux pumps and changes in drug targets (Costa-de-Oliveira & Rodrigues, 2020; Rodrigues, Silva & Henriques, 2014). A mutator phenotype resulting from defects in the mismatch repair gene MSH2 has been discovered in a large proportion of clinical samples, facilitating the acquisition of multidrug resistance (Healey *et al*., 2016). Identifying C. glabrata infections poses several difficulties. This species' ability to evade host immune responses and survive intracellularly complicates detection (Lewis, Viale & Kontoyiannis, 2012). Furthermore, phenotypic susceptibility testing can result in misclassifying resistant strains, as evidenced by fluctuating MICs around breakpoints and the presence of resistance in strains with wild-type FKS genotypes (Aldejohann *et al*., 2022). These factors highlight the necessity of combining various diagnostic methods, including molecular techniques such as FKS genotyping, to accurately identify and characterise *C. glabrata* infections (Ho *&* Haynes, 2015).

Treatment Strategies

Current antifungal therapies

The primary treatments for Candida glabrata infections currently include azoles, echinocandins, and amphotericin B. However, *C. glabrata* presents substantial therapeutic challenges due to its decreased sensitivity to azoles and growing resistance to echinocandins (Rasheed, Battu & Kaur, 2020). While fluconazole is frequently used, it may be less potent against C. glabrata compared to other Candida species (Montravers *et al*., 2011). For treating C. glabrata infections, echinocandins such as anidulafungin and caspofungin are often the preferred choice, particularly in cases of azole resistance (Montravers *et al*., 2011; Vella *et al*., 2017). Researchers are investigating combination therapies to improve treatment effectiveness. For instance, catechin, a naturally occurring polyphenolic compound, has exhibited synergistic effects when used in conjunction with miconazole against both susceptible and azole-resistant *C. glabrata* strains (Hervay *et al*., 2023). Furthermore, berberine, a benzylisoquinoline alkaloid, has shown promise as a combinatorial nutraceutical adjuvant, enhancing the effects of traditional antifungal medications (Gupta, Gupta & Poluri, 2021). In summary, although current antifungal therapies for *C. glabrata* infections mainly rely on azoles and echinocandins, the rising prevalence of drug-resistant strains necessitates the development of innovative treatment approaches. Combination therapies and natural products represent promising avenues for improving antifungal efficacy against this challenging pathogen.

Combination Therapies

Combination therapies have shown promise in treating *Candida glabrata* infections, particularly because of their increasing resistance to traditional antifungal agents. The combination of catechin, a natural polyphenolic compound, with miconazole resulted in complete growth inhibition of sensitive *C. glabrata* strains and a significant growth reduction in azole-resistant clinical isolates (Hervay *et al*., 2023). This synergistic effect was attributed to the increased intracellular ROS generation and changes in plasma membrane permeability. The combination of isavuconazole with micafungin demonstrated synergistic interactions with several Candida species, including *C. glabrata*, as shown by bliss independent drug interaction analysis and time-kill assays (Katragkou *et al*., 2017). However, the combination of isavuconazole and amphotericin B showed antagonistic effects against *C. glabrata*, highlighting the importance of the careful selection of drug combinations.

Novel therapeutic targets and approaches

The increased drug resistance and biofilm formation ability of *C. glabrata* are major obstacles to the development of effective treatments, and several novel therapeutic targets and approaches have been identified to combat *C. glabrate infections* Natural products, such as catechins, show promise in combination therapies. When used with miconazole, catechin inhibits the growth of sensitive *C. glabrata* and reduces the growth of azole-resistant isolates by increasing intracellular ROS generation and altering plasma membrane permeability (Hervay *et al*., 2023). Another natural compound, geraniol, has demonstrated potent anti-biofilm activity against *C. glabrata* by targeting multiple cellular pathways, including cell wall components, membrane ergosterol, and ABC drug efflux pumps (Gupta, Gupta & Poluri, 2021). The glyoxylate cycle gene ICL1 has been identified as crucial for *C. glabrata* survival in macrophages and virulence in vivo, suggesting that antifungal drugs targeting fungal Icl1 may be potential therapeutic interventions (Chew *et al*., 2019). Additionally, the transcription factor CgRpn4 has been shown to regulate ergosterol biosynthesis and contribute to azole resistance, thereby presenting another potential drug target (Pais *et al*., 2020).

Epidemiology and Transmission

Global distribution and prevalence

Candida glabrata has become a significant nosocomial pathogen worldwide, ranking second among Candida species that cause bloodstream infections in numerous regions. The incidence of this condition varies by location; for instance, a Thai study found that C. glabrata constituted 29.6% of Candida bloodstream isolates (Boonsilp *et al*., 2021). In Switzerland, the proportion of C. glabrata has risen markedly from 18% to 27% over a 15-year span (Adam & Khan, 2021). Notably, population genetic research has uncovered both clonal expansion and recombination in C. glabrata, with five primary populations identified in the United States, showing minimal genetic differentiation between geographic areas (Lott, Frade & Lockhart, 2010). However, in Qatar, substantial genetic diversity has been observed within hospitals, with indications of recombination, inbreeding, and clonal expansion (Perez-Lopez *et al*., 2024). Such diversity implies that *C. glabrata* can propagate clonally within healthcare environments and through genetic mixing. In summary, *C. glabrata* exhibits a global distribution with increasing prevalence in many areas. Its population structure demonstrates characteristics of both clonal and sexual reproduction. Transmission appears to occur both within hospitals and through wider dissemination, likely facilitated by human movement and migration. Continuous surveillance is crucial for tracking the evolving epidemiology and emergence of drug resistance in this opportunistic pathogen.

Risk factors for infection

Candida glabrata has become a notable hospital-acquired pathogen, with various factors contributing to its rising prevalence. Extended hospital stays, especially in critical care units, and previous antibiotic usage have been recognised as key risk factors for nosocomial *C. glabrata* infection (Vazquez *et al*., 1998). Additional significant risk factors encompass compromised immunity, cancer treatment, use of broad-spectrum antibiotics, and the presence of indwelling vascular catheters (Giri, Kindo & Kalyani, 2014; Richardson, 2005). Notably, age and denture use have been linked to concurrent infection with C. albicans and *C. glabrata* in oral candidiasis patients, with multivariate analysis showing that denture

use and immunosuppressive therapy substantially increased the likelihood of co-infection with these two Candida species (Hato *et al*., 2022). Moreover, abdominal surgery and total parenteral nutrition have been associated with C. glabrata infections (Rajendran *et al*., 2016). In summary, the epidemiology of C. glabrata infection is multifaceted and influenced by various host and environmental elements. The possibility of external nosocomial acquisition, including from the hospital environment, has been proposed (Vazquez *et al*., 1998). Furthermore, genomic research has uncovered evidence of recombination, inbreeding, and clonal expansion within and between hospitals, including nosocomial transmission among COVID-19 patients (Perez-Lopez *et al*., 2024). These discoveries underscore the importance of infection control measures and prudent antimicrobial use in healthcare environments to prevent the spread of *C. glabrata.*

Hospital-acquired infections and outbreaks

Candida glabrata has emerged as a significant cause of hospital-acquired infections, particularly in critically ill and immunocompromised patients. It is the second most common Candida species associated with invasive candidiasis after *C. albicans* (Hassan, Chew & Than, 2021). The incidence of *C. glabrata* infection in hospitalised patients has been increasing, partly because of its intrinsic and acquired resistance to fluconazole and other azole antifungal agents (Ho & Haynes, 2015; Lin *et al*., 2005). Interestingly, *C. glabrata* is phylogenetically more closely related to non-pathogenic Saccharomyces cerevisiae than to other Candida species; however, it has evolved to become an opportunistic pathogen (Ho & Haynes, 2015). This highlights the complex nature of its virulence mechanism*. glabrata* infections are associated with high mortality rates, with one study reporting a crude mortality rate of 60 % in ICU patients (Tortorano *et al*., 2012). Hospital-acquired *C. glabrata* infections are often associated with specific risk factors and medical interventions, and patients receiving total parenteral nutrition, broad-spectrum antibiotics, indwelling catheters, or recent surgery are at higher risk (Barac *et al*., 2020). A case-control study found that exposure to certain antibacterial agents, specifically vancomycin and piperacillin-tazobactam, was associated with an increased risk of *Candida glabrata* candidemia (Lin *et al.,* 2005). Additionally, biofilm formation, tolerance to high-stress environments, and resistance to neutrophil killing contribute to *C. glabrata* persistence in healthcare settings (Perez-Lopez *et al*., 2024).

Discussion

Clinical relevance of Candida glabrata has risen dramatically in the last few decades in relation to their peculiar capacities in adapting, being pathogenic, and developing resistance. Unlike C. albicans, the less virulent pathogen C. glabrata does not possess classical virulence characteristics such as filamentation and secreted proteolytic enzymes but is still a significant pathogen in immunocompromised individuals (Hu *et al*., 2022; Eliaš & Gbelska, 2022). The pathogen possesses high levels of adaptability to and persistence in challenging host environments, featuring genomic plasticity, metabolic flexibility, strong stress responses, and an extraordinary ability to form biofilms. These mechanisms together contribute to its pathogenic strength and treatment difficulty (Padder *et al., 2*022).

C. glabrata is an example of an organism adapted by means of genetic plasticity, allowing a prompt reaction to environmental stresses, including drug pressure. Mutations in genes, for instance MSH2, lead to mutator phenotypes, which increase the evolutionary capacity to become resistant (Healey *et al.,* 2016). Copy number variation, chromosome arm conversion and the accumulation of nonsynonymous mutations in adhesin genes also suggest in-host adaptation (Carreté *et al.,* 2019). Metabolically, C. glabrata has evolved responses that promote growth under conditions of nutrient limitation, including the glyoxylate cycle, iron transporter regulation, and the repression of alternative carbon source utilisation, which are important during intracellular infection (Seider *et al.,* 2014; Chew *et al*., 2019).

The virulence of C. glabrata is highly dependent on its adhesion to host tissues and medical devices, a property that is achieved through a large family of adhesins, especially the EPA gene family. EPA1, in particular, confers tight epithelial adhesion and is required for colonisation. C. glabrata, while not able

to trigger robust inflammatory responses, is capable of surviving and replicating within macrophages, avoiding immune detection and having a role in the persistence of infection (Kasper Seider & Hube, 2015). The control of virulence factors is highly interconnected with environmental sensing and stress response at multiple levels. Environmental defences against oxidative stress and intracellular persistence are controlled by transcription factors including Yap1, Skn7 and Msn4 (Roetzer, Gabaldón, & Schüller, 2011).

Mechanisms of resistance in C. glabrata are diverse and frequently multifactorial. This high inherent resistance to azoles is mainly the result of the overexpression of ATP-binding cassette (ABC) transporters, including CDR1 and CDR2, as well as the presence of mutations in ERG11 and its transcriptional regulator UPC2 (Czajka *et al*., 2023). Resistance to echinocandins, which is becoming more frequent in the hospital environment, is predominantly caused by mutations in the FKS1 and FKS2 genes, which are targets of the β-1,3-glucan synthase essential for cell wall integrity (Pemán, Cantón & Espinel-Ingroff, 2009). The MDR phenotype, especially among isolates into which MSH2 mutations were introduced, is a major concern for therapy protocols and emphasises the importance of monitoring at the molecular level (Healey *et al.,* 2016).

Biofilm development is an important factor in the resistance and persistence of C. glabrata. Biofilms formed on medical devices offer a protected environment limiting penetration of antifungals through the biofilm but also promoting cell-cell communication, thereby improving survival and virulence. Regulons of Yak1 kinase and the Swi/Snf chromatin-remodelling complex were reported in biofilm-associated resistance and expression regulation of major adhesins EPA6 and EPA7 (d'Enfert & Janbon, 2016).

Future Research

Further research should aim to define molecular crosstalk in regulatory networks contributing to biofilm formation, stress adaptation and resistance development in Candida glabrata. Studying host-pathogen interactions at the molecular level and identifying new drug targets could benefit diagnosis and treatment, especially from multidrug-resistant clinical isolates in specimens.

Conclusion

Candida glabrata has become a formidable pathogen due to its adaptability, pathogenic attributes, and drug resistance. Unlike *C. albicans*, it compensates for the absence of morphological transition through adhesins, stress response pathways, and intracellular survival within host immune cells. Its genetic plasticity and high mutator phenotype enable resistance and adaptation to medical treatment. Biofilm formation further enhances its resistance and survival in nosocomial environments. Current therapeutic options are limited, and resistance to first-line antifungal drugs is increasing. The molecular mechanisms underlying its adaptation, virulence, and resistance remain to be fully understood. Improved therapies and diagnostics for *C. glabrata* are critical to combating infections and enhancing patient outcomes.

Conflict of Interest

The authors declare that they have no competing interests.

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