Candida albicans and *Candida glabrata*: global priority pathogens

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SUMMARY

A significant increase in the incidence of *Candida* mediated infections has been observed in the last decades, mainly due to rising numbers of susceptible individuals. Recently, the World Health Organization (WHO) published its first fungal pathogens priority list, with *Candida* species listed in medium, high, and critical priority categories. This review is a synthesis of information and recent advances in our understanding of two of these species – *C. albicans* and *C. glabrata*. Of these, *C. albicans* is the most common cause of candidemia around the world and is categorized as a critical priority pathogen. *C. glabrata*

is considered a high priority pathogen and has become an increasingly important cause of candidemia in recent years. It is now the second most common causative agent of candidemia in many geographical regions. Despite their differences and phylogenetic divergence, they are successful as pathogens and commensals of humans. Both species can cause a broad variety of infections, ranging from superficial to potentially lethal systemic infections. While they share similarities in certain infection strategies, including tissue adhesion and invasion, they differ significantly in key aspects of their biology, interaction with immune cells, host damage strategies, and metabolic adaptations. Here we provide insights on key aspects of their biology, epidemiology, commensal and pathogenic lifestyle, interactions with the immune system, and antifungal resistance.

INTRODUCTION

The World Health Organization (WHO) recently announced its first ranking of priority groups for fungal pathogens based primarily on "concerns over drug resistance and/or treatment management" (https://www.who.int/publications/i/item/9789240060241). This WHO report stresses the threat fungal pathogens pose to public health, especially to immunocompromised patients, with a growing resistance to treatment and a limited number of classes of available antifungal drugs. Of the nineteen fungal species in the report, *C. albicans* was listed along with *C. auris* amongst the four "critical priority pathogens", and *C. glabrata* was categorised amongst seven "high priority pathogens" (along with *C. tropicalis* and *C. parapsilosis*). *C. glabrata* is a very distant phylogenetic relative of *C. albicans* and has been reclassified and renamed within the new *Nakaseomyces* genus, along with three sister species, and is now called *Nakaseomyces*

glabratus. *C. glabrata* is a very distant phylogenetic relative of *C. albicans* and has been reclassified and renamed within the new *Nakaseomyces* genus, along with three sister species, and is now called *Nakaseomyces glabratus* (1). There has been some opposition to reclassifying *C. glabrata* to *N. glabratus* on the basis that it may "dilute the importance of *Candida* as a major human group of pathogens" and that "it engenders uncertainty, difficulties in messaging and hampers advocacy" (Denning, in press). On the other hand, it has been pointed out that the phylogenetic distance between *N. glabratus* and *C. albicans* is double that of humans to snakes. This distance is reflected in divergences in multiple phenotypes including susceptibility to fluconazole and other aspects of pathobiology (summarized in detail in this review). Therefore, it may be better to clearly differentiate these two organisms than confuse them as broadly similar species of yeast within the same genus (2, 3). For the purpose of this review we will retain the use of *C. glabrata* to be consistent with the relevant cited literature, whilst recognizing that we are in a period of phylogenetic revision that will see *C. glabrata* transitioning to a new name that reflects its true phylogeny.Despite the evolutionary distance between *C. albicans* and *C. glabrata*, there are some shared characteristics and pathologies, and this review focuses on a comparison of the biology and pathogenesis of these two pathogens.

About thirty species that have previously assigned within the *Candida* genus can cause human disease. Of these, *C. albicans* and *C. glabrata*, together with *C. parapsilosis* and *C. tropicalis*, represent the most common causes of invasive disease. The WHO emphasizes the need for a better understanding of the disease burden and antifungal resistances, and for an improvement of diagnostics and treatments (4).

Both *C. albicans* and *C. glabrata* cause a range of disease manifestations. Mucosal candidiasis including vaginitis is most commonly caused by *C. albicans*, followed by *C. glabrata*, and the global burden of recurrent *Candida* vaginitis (defined as more than four episodes per year) is estimated to be between 103–172 million annually (5). The incidence of systemic candidiasis is typically around 2–21 per 100,000 people, with numbers varying considerably depending on geography and various patient factors (Figure 1). *Candida* species normally rank in the top four causes of bloodstream infections along with *Staphylococcus aureus*, coagulase-negative staphylococci, and *Enterococcus* spp. (6, 7). Associated mortality due to invasive candidiasis can be 40–75% in different health care settings, accounting for a total of around 250–700,000 systemic infections and 50–100,000 deaths / year (6-9). Typically, *C. albicans* accounts for around 40–80% of *Candida* isolates recovered from patients in hospitals, whilst *C. glabrata* represents only about 5-30% of such isolates although these figures vary geographically. (10-12) . However, more recently *C. glabrata* isolation rates have increased in a number of settings in different countries to 2–28% of *Candida* species isolates — perhaps due to the high number of azole and echinocandin resistant strains (13).

Candida species have long co-existed with humans as commensals and infectious agents. Hippocrates described oral candidiasis (thrush) as early as 200 BC, but the first scientific studies dealing with *C. albicans* and *C. glabrata* took place in the late twentieth century (14). A mycotic association for vaginal infection was first shown for *C. albicans* in 1849, and in 1917 for *C. glabrata* (15). More recently climate change has been suggested as a

factor in the sudden worldwide appearance of *C. auris* as a pathogen (16). Vaginal infections with *C. albicans* are extremely common in otherwise healthy women (11), and *C. albicans* is responsible for the vast majority of these infections. The incidence of invasive infections with *Candida* species is higher in individuals with impaired immunity, be it due to treatments required for organ transplants, malignancies, or other immunosuppressive regimens. Indeed, there has been an increase in susceptible individuals in modern times due to the development and widespread use of treatments that lead to immunosuppression (17). Other common predisposing risk factors for systemic candidiasis are the use of antibiotics, chronic kidney disease, presence of central venous catheters, blood transfusions, and extended stays in the intensive care unit (ICU) (18, 19). In summary, *C. albicans* and *C. glabrata* represent two major agents of superficial and systemic human disease of global health care concern.

Distant cousins with distinct characteristics

The genus *Candida* comprises approximately 200 taxonomically diverse species with many different lifestyles and morphologies (14). Most species associated with humans are harmless commensals, but at least 30 can cause human infections (20). Five species are responsible for over 90% of infections: *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*, ranked from the most common to the least, although regional differences exist (17, 21). The most common, *C. albicans* and *C. glabrata*, are frequently isolated as commensals from skin surfaces and mucosal surfaces, in particular the GI tract (22).

Even though they share a similar commensal lifestyle, *C. albicans* and *C. glabrata* are distinct in many other aspects — summarized here and described in detail below. They are widely divergent phylogenetically. *C. glabrata* is taxonomically closer to *Saccharomyces cerevisiae* (baker's yeast) than to *C. albicans*. *C. albicans*, together with other important *Candida* species such as *C. parapsilosis* and *C. tropicalis*, is part of the so-called "CTG clade" in which the CTG codon codes for leucine instead of serine. (1). Genetically, *C. albicans* is a diploid fungus (23), although haploid forms have been generated that are stable enough to create haploid mutant libraries (24). *C. glabrata* is a haploid organism for which no sexual cycle has been described so far (25) (see below). Phenotypically, *C. albicans* is polymorphic, being able to transition reversibly between yeast, hyphae, and pseudohyphae, which is a key aspect of its pathogenesis (26, 27). In addition, *C. albicans* can grow as other distinct phenotypic forms including white, grey, opaque, and GUT cells (see below) (Figure 2). In contrast, *C. glabrata* grows almost exclusively in the yeast form and does not depend on morphological changes to promote infection (28, 29). Both *Candida* species are able to form biofilms, although the mechanisms they use for this differ (30, 31). The two fungi share common adhesion strategies reliant on large families of adhesins — for example the Als proteins in *C. albicans* (32) and Epa proteins in *C. glabrata* (33).

During infections, fungi need to acquire nutrients to survive and grow. *C. albicans* has no known auxotrophies [except biotin (34)] and it is equipped with a broad range of secreted hydrolases and a cytolytic peptide toxin, that are able to break down host tissue for nutrients (35-37) (Sprague *et al.*, submitted for revision). In contrast, *C. glabrata* is auxotrophic for

biotin, pyridoxine, nicotinic acid, and thiamine and only has a limited array of secreted proteases (28, 34), but has a range of GPI-anchored cell surface-associated yapsin proteases with a broad range of functions (38-40). Within macrophages, both species can cause a delay in phagosome maturation (41, 42), but only *C. albicans* forms hyphae that contribute to phagocyte escape (43). *C. glabrata* appears to multiply inside the phagosome until the high fungal load leads to rupture of the phagocyte (42). In conclusion, within *Candida* species, and especially for *C. albicans* and *C. glabrata*, the strategies to survive, grow, and cause damage in the host differ significantly. This is discussed in more detail below.

CLINICAL ASPECTS

Epidemiology

Long-term surveillance programs, such as the ARTEMIS DISK epidemiological study, which compiled data from 41 countries over more than 10 years (20), and the SENTRY antimicrobial surveillance program (44), have documented changes in the demographic and geographical incidence and impact of *Candida* spp. Across these studies, the five major species responsible for most *Candida* infections are generally found in all geographical regions, but with different relative distributions (Figure 1). In most regions and studies, *C. albicans* is the most prevalent species (20). However, the two past decades have seen a shift in prevalence from *C. albicans* to "non-*Candida albicans" Candida* (NCAC) species, which may in part be due to improved identification methods. For example, in a study about bloodstream infections caused by *Candida* species in Shanghai, NCAC species outnumbered *C. albicans* (45). In the SENTRY antimicrobial surveillance 2008–2009, *C. albicans* was the most frequently detected *Candida* pathogen, but again the frequency

of NCAC species differed according to geographical region. *C. parapsilosis* was found to be the second most common *Candida* species in the Asia-Pacific area, and *C. glabrata* in other regions (44). Additionally, in another study *C. tropicalis* was the main cause of candidemia in Western India, followed by *C. parapsilosis* (46). In Greece, *C. parapsilosis* was responsible for most infections in patients with haematological malignancies (47). Thus, distribution of NCAC species can vary greatly between different continents, but also within regions of the same continent and depending on the patient cohort (13).

C. albicans and *C. glabrata* can both be found, albeit infrequently, in the environment: *C. glabrata* has been detected on plants, feces from yellow-legged gulls, and in soil (48, 49). *C. albicans* is rarely found in the environment, but recently has been isolated from soil, the barks of trees, and pigeon droppings (49-52). Zoonotic transmission of *Candida* spp. is rare, but its potential cannot be ignored. *Candida* species can be detected and cause disease in domesticated animals including dogs and cats, but also in a very wide range of wild animals and birds (53). Animal risk factors are similar to those in humans — e.g. immunosuppressive disorders — and isolates from humans and animals seem to have no host-specific genotypes or host species-specific lineages (54). This suggests that animals may serve as reservoirs for human infection. In conclusion, *Candida* spp. are widely distributed and are able to infect both humans and a wide range of other species, and they can occur in natural environments without obligatory associations with animals.

Diagnosis

In general, for clinical treatment and management of *Candida* and other fungal infections, a late diagnosis equates to a poor prognosis (55). Therefore, accurate and sensitive

diagnostics are critical for effective clinical management of invasive disease. *C. albicans*, *C. glabrata*, and other *Candida* yeasts can, however, cause a variety of infections: ranging from skin, vaginal or oral candidiasis to severe chronic forms of granuloma or life-threatening blood stream infections and invasive candidiasis, and the optimal diagnostic tool reflects the severity and urgency of the infection that is to be treated. The type of disease is linked to a wide number of predisposing factors: pregnancy, diabetes, infancy or old age, hospitalization, catheterization, trauma, transitory, and chronic or genetic immune deficiency. In addition, diet, denture wearing, certain surgical interventions and other stresses are also implicated in affecting *Candida* spp. disease prevalence and severity (7, 56). Some of these predisposing factors increase susceptibility to specific *Candida* spp. infections. For example, denture wearing increases the likelihood of oral candidiasis and pregnancy that of vaginal candidiasis.

A broad range of options are available to diagnose *C. albicans* and/or *C. glabrata* and other yeast infections that differ in their accuracy, speed, specificity and sensitivity (57). Some of these diagnostic tests have been developed to be performed by non-specialists and are available at “point of care” whilst others require the back up of sophisticated high-technology analytical methods, such as polymerase chain reaction (PCR), DNA-sequencing-based approaches, or protein fingerprinting by (MALDI-TOF) mass spectrometry. Currently, microscopy and culture from normally sterile or non-sterile body sites represent the gold standard for diagnostic tools in the detection of yeast infections. Fungal selective or indicator growth media such as Sabouraud agar, CHROMagar, chocolate or blood agar are used to narrow down the identification of the yeast species. For

example, the chromogenic CHROMagar™ *Candida* test generates green colored colonies for *C. albicans* and mauve colonies for *C. glabrata* (58). Culturing *Candida* spp. from the bloodstream or other sites will routinely take 24 h or more but will yield an organism that can then be identified and subjected to specific susceptibility testing. However, more rapid tests are also required for urgent diagnoses. Blood samples can be tested directly *via* the T2Candida Panel and the T2Dx Instrument (T2Candida) (57). Other tests, such as Platelia™ Candida Ag Plus EIA (Bio-Rad, Marnes-la-Coquette, Paris, France) and the CandTec latex agglutination test (Ramco Laboratories, Stafford, TX, USA), can quickly detect components (yeast wall and/or metabolites) of fungal cells as biomarkers of infection. However, biomarker tests are normally not able to discriminate between different *Candida* species, which may be important in determining the most appropriate treatment. Biomarker tests can be complemented by use of serological assays to detect the host antibody response including immunodiffusion, counter-immunoelectrophoresis, enzyme-linked immunosorbent assays (ELISA), complement fixation (CF), lateral flow assays, radioimmunosorbent assays (RIA) or agglutination assays, which again will not be species-specific. Such tests are, however, normally only available in specialized fungal diagnostic laboratories and serological tests often lack sensitivity, especially when used for immunocompromised patients. General fungal diagnostics such as those detecting fungal (1,3)-β-D-glucan (BDG) are useful, rapid, and highly sensitive, but they lack specificity for species or even genus differentiation, essential information for the selection of an appropriate antifungal treatment. In the future, this array of diagnostic formats may be complemented by ultrasensitive laser-based biophysical biosensors with high fidelity and sensitive detection of novel biomarkers (59).

Types of Infection

Candida spp. infections are divided into two broad categories: superficial and systemic (Figure 1). Superficial infections are those of the skin or mucosal surfaces of the body e.g., oropharyngeal, esophageal, vulvovaginal, and cutaneous candidiasis. Superficial infections are usually non-life threatening and can mostly be treated with topical antifungals with a high success rate (60). However, even though esophageal candidiasis is a superficial infection, it requires a systemic therapy (61).Vulvovaginal candidiasis affects 80% of women once in their life (62) and cutaneous candidiasis accounts for 7% of all inpatient visits to dermatologists (63). Additionally, recurrent vulvovaginal candidiasis (RVVC) affects 9% of women with severe impact on life quality (64). Chronic mucocutaneous candidiasis (CMC) is a recurrent superficial infection of mucous membranes, skin and nails and usually affects immunodeficient patients with a range of defined genetic polymorphisms (63).

Systemic infections are disseminated and can affect nearly all internal organs. Under immunosuppression, systemic *Candida* spp. infections can originate from the commensals that reside in the gastrointestinal (GI) tract (65) or from external sources, e.g., central venous catheters (66). Systemic *Candida* spp. infections can affect the heart, brain, kidneys, and many other organs *via* the bloodstream (candidemia). The mortality rate of such *Candida* spp. bloodstream infections ranges between 30-60% (67, 68). A serious manifestation of systemic infection caused by *Candida* species is sepsis. *Candida* spp. are responsible for about 5% of all reported sepsis cases, and when septic shock develops, it is fatal in more than half of the cases (69). This is exacerbated by late diagnosis and delayed

antifungal treatment (70). In rare cases, a superficial infection can lead to a secondary systemic infection. Such secondary *Candida* spp. infections can also occur following bacterial infections or sepsis, and they result in prolonged ICU stays, increased mortality, and considerable healthcare costs (71). In summary, *Candida* spp. infections can be seen as a broad spectrum of conditions that ranges from non-life threatening superficial to systemic infection often associated with high mortality.

Candida species also can exacerbate or become exacerbated by other existing diseases. The COVID-19 pandemic has led to an increased incidence of candidemia (72), and COVID-19 patients tend to have a reduced cytokine response to *C. albicans* (73) and have longer stays in the ICU (74). Human immunodeficiency virus (HIV)-positive patients suffer more commonly from oral candidiasis and/or esophageal candidiasis (in case of low CD4+ counts), but HAART therapy has significantly reduced oral and esophageal candidiasis rates and *Candida* spp. colonization in HIV-positive individuals (75, 76). Recently it was shown that patients with severe Covid-19 have a proliferation of *C. albicans* in the gut. That leads in turn to significantly increased recruitment and NETosis of neutrophils in the lung, thereby exacerbating lung damage (77). This damage was mitigated by antifungal treatment or IL-6 receptor blockade. Patients with diabetes mellitus (DM) are more susceptible to oral (78) or vulvovaginal (79) candidiasis. This can be attributed to altered physiological factors in diabetic patients, such as higher concentrations of blood glucose, a weakened immune system, and increased *Candida* spp. adherence to epithelial cells in this setting (80). In addition, *Candida* species can promote other diseases. For example, multiple types of gastrointestinal cancers (e.g., stomach and colon cancer) have been linked

to the presence of *Candida* spp. cells in the GI tract, which has also been associated with an increased risk of metastasis (81). *C. albicans* strains with different capacity to cause damage were also found in the gut of IBD patients, and the high-damaging strains induced proinflammatory immunity through the peptide toxin candidalysin, which may contribute to the disease (82). In conclusion, the pathogenic potential of *Candida* species increases in patients with impaired immune responses and can also contribute to the severity of a range of diseases.

Antifungal Treatment

Oral fluconazole, miconazole or nystatin are commonly used as first line antifungal agents for oral thrush caused by *Candida* species. However, many *C. glabrata* strains have a low susceptibility or genetic resistance to fluconazole and will fail to clear a mucosal infection on a low dose fluconazole. Serious oral or oropharyngeal infections may be treated with a 2-week course of an echinocandin (caspofungin, micafungin or anidulafungin) but as intra venous (i.v.) agents these are not appropriate for managing less invasive disease. Vaginal infections with this yeast are often managed with longer courses of topical antifungals such as miconazole or nystatin or occasionally a 2-week course of oral voriconazole for recalcitrant infections depending on susceptibility (83, 84). In the future ibrexafungerp, a triterpene with a similar action to the echinocandins, but active after oral administration, may prove helpful in these cases (84). For systemic invasive *Candida* spp. disease an i.v. administration of an echinocandin is normally recommended (85) as initial therapy, although fluconazole may be an appropriate continuation therapy for susceptible patients. For *C. glabrata* isolates identified as susceptible-dose-dependent to fluconazole, a high dose (800 mg/d) is normally recommended although IDSA guidelines recommend the use

of an echinocandin as a first line therapy, with fluconazole used only after the patient has responded to an echinocandin. Rezafungin, a new echinocandin that persists longer in the bloodstream and may only require i.v. administration on a weekly basis, could prove to be beneficial in the future (86). Systemic infections due to *C. glabrata* that are resistant to both azoles and echinocandins can be particularly problematic to treat. These infections may require administration of amphotericin B with or without flucytosine as alternative agents (85).

Antifungal Resistance — Biological and Clinical Principles

Both *C. albicans* and *C. glabrata* pose clinical challenges due to a range of drug resistant phenotypes that challenge the efficacy of existing and future generations of antifungal drugs, in particular for treatment of systemic infections (6, 87-90). Increasing resistance to antifungals is normally the consequence of the rise in prevalence of *Candida* species and strains with intrinsic resistance — such as with fluconazole-resistant *C. glabrata* strains — but can also be due to *de novo* induction of resistance in isolates from species that are normally drug susceptible, which is common for *C. albicans.* Typical surveillance data show that fluconazole resistance exists in approximately 8% of *C. albicans* strains, but as many as 26% of strains of *C. glabrata* (91).

C. albicans is the most commonly implicated *Candida* species in candidaemia, although *C. glabrata* exceeds *C. albicans* in prevalence in fluconazole-resistant candidaemia cohorts (92). In the clinic, *C. glabrata* is also increasingly commonly displaying echinocandin resistance, where resistance can vary between 2 and 12% of isolates in different hospitals. Some of these strains may be regarded as multiple drug resistant (MDR)

due to co-resistance to fluconazole (87, 93). Approximately 14% of fluconazole-resistant *C. glabrata* isolates are also resistant to one or more echinocandins. These azole/echinocandin cross-resistant strains are often *ERG3* mutants that harbor additional *FKS* gene mutations (see below). Patients infected with these strains fail to respond to both echinocandin and azole treatments (85, 91, 94).

Newer drugs flowing into the yeast-active antifungal pipeline include rezafungin, isavuconazole, ibrexafungerp, opelconazole, and fosmanogepix. All these novel antifungals have activity against both *C. albicans* and *C. glabrata* (95, 96). Rezafungin is a stable echinocandin that only requires once weekly i.v. administration; ibrexafungerp is a new triterpenoid pharmacophore, and fosmanogepix is an inhibitor of the Gwt1 enzyme that is required for GPI-anchoring of proteins into the cell wall (95). Olorofim, another new class of antifungal drug that inhibits the enzyme dihydroorotate dehydrogenase, has no activity against either of these two species of *Candida*.

In recent years it has become clear that emergent resistance can be distinguished from "heteroresistance" and "tolerance" of a fungus to an antifungal drug (88). Heteroresistance refers to fungal strains where a small number of cells have a much higher minimal inhibitory concentration (MIC) to a specific drug than the significant majority of cells in a given population. Heteroresistance is distinguishable from tolerance (also called "trailing growth" in the clinical literature), which is the ability of a sub-population of a generally susceptible and isogenic strain to grow slowly in drug concentrations that are well above the MIC (85, 88). Tolerance seems to involve the chaperone Hsp90, the calcineurin

pathway, and protein kinase C (Pkc) (88). Both heteroresistance and tolerance are relevant to drug susceptibility of both *C. albicans* and *C. glabrata*.

Clinical strategies to mitigate the challenges imposed by drug resistant and tolerant *Candida* spp. strains and species in general have to consider existing and new-in-the-pipeline antifungals that have different spectra of activity. Clinical trial data and a range of possible classical mechanisms of resistance as well as heteroresistance and tolerance mechanisms also need to be considered for optimal clinical decision making (85, 90). This may require standardized tests to be devised that will allow to take heteroresistance and drug tolerance into account when making clinical decisions about the choice of an antifungal.

Genetic and Molecular Basis for Resistance

Antifungal resistance in *C. albicans* and *C. glabrata* can involve a wide range of mechanisms. These include reduced drug uptake, overexpression of drug efflux transporters or the targets of azole or echinocandin antifungals, target site mutations, chromosomal aneuploidies, isochromosome formation, loss of heterozygosity, and other changes that collectively affect the drug resistance profile (88, 93, 97-106). Some of these mechanisms are also important to the resistance profile of *C. nivariensis*, and *C. bracarensis* — two sibling species in the *C. glabrata* complex (107, 108). Some antifungal mechanisms also affect or intersect with those affecting virulence attributes such as adhesion, biofilm production, thermotolerance, resistance to immune cells, and the cell wall proteome (102, 103, 109). For example, fluconazole and exposure to macrophages

406 can confer a cross-resistance between antifungals and immune cells *via* the emergence of
407 *petite* strains of *C. glabrata* (110-112).
408
409 Currently the key drugs used in the clinic are azoles, which interfere with ergosterol
410 biosynthesis in the cell membrane, and echinocandins, that inhibit cell wall β-1,3 glucan
411 biosynthesis. Resistance to azoles can occur through mutations in the primary azole target,
412 Erg11/Cyp51, which encodes lanosterol 14α-demethylase. This leads in turn to changes in
413 the flux through the ergosterol biosynthetic pathway and the accumulation of the toxic
414 sterol intermediate, 14α-methyl-3,6-diol, that is produced by Erg3 — a C-5 sterol
415 desaturase. In *C. albicans* and *C. glabrata* loss-of-function mutations in *ERG3* can also
416 confer MDR properties (93). Gain-of-function mutations in the ergosterol pathway
417 transcription factor gene *UPC2* lead to overexpression of *ERG11*, and isochromosome
418 formation [i(5L) in *C. albicans* which leads to amplification of *ERG11* and *TAC1* (113)]
419 and other aneuploidies can also increase *ERG11* expression by altering the copy number
420 of the *ERG11* gene (114). In *C. albicans*, trisomies in chromosomes 3 and 4 are associated
421 with fluconazole resistance, and an increased expression of *CgCDR1* can be associated
422 with aneuploidy in *C. glabrata* (115, 116). Also, mutations in *C. albicans ERG11*
423 commonly confer increased azole resistance, whilst target site *ERG11* mutations are rare
424 in *C. glabrata*.
425
426 Azole resistance can also be due to upregulation of genes encoding azole efflux pumps
427 (*CaCDR1*, *CaCDR2* and *CaMDR1*) and their transcriptional regulator genes (*CaTAC1* for
428 *CaCDR1* and *CaCDR2*, and *CaMRR1* for regulation of *CaMDR1*). In *C. glabrata* CgPdr1

regulates the efflux systems encoded by *CgCDR1*, *CgCDR2*, and *CgSNQ2*, and upregulation of *CgPDR1* confers azole resistance (88, 93, 98, 100, 103, 105, 106, 117). In *C. glabrata* mutations in *CgCNE1* and *CgEPA13* have also been implicated in drug resistance (118) . Gain-of-function mutations in the ergosterol pathway transcription factor gene *UPC2* (*C. albicans*)/ *UPC2A* (*C. glabrata*) leads to overexpression of *ERG11* in both species (119, 120).

The target of echinocandins is the catalytic subunit for β-1,3-glucan biosynthesis, (1,3)-β-D-glucan synthase (FKS/GLS), in the cell membrane. Echinocandin-resistant mutants usually involve mutations in the *FKS* genes that encode this protein. In *C. albicans* these mutations occur in two "Hot Spots" (HS) in the *CaFKS1* gene rather than in *CaFKS2* and *CaFKS3*, whilst in *C. glabrata* HS mutations that effect echinocandin MICs occur in both, *CgFKS1* and (more commonly) *CgFKS2* (94, 121, 122).

In the cell wall of *Candida* species both chitin and β-1,3-glucan contribute to structural strength. *Candida* species can also upregulate chitin synthesis as a response to damage of β-1,3-glucan, which leads to strengthening of the wall and reduced sensitivity to echinocandins (123-125). This is a reversible process that occurs *in vitro* and likely *in vivo*. Because this is a reversible phenotypic adaptation and not a mutation, it may not change the *in vitro* MIC when the strain is isolated from the patient and grown on non-drug selective conditions on agar (126). The higher levels of chitin in these echinocandin-adapted strains may affect the immune response to the surviving cell population, potentially rendering them less inflammatory (122, 127). High levels of chitin can explain the

452 "paradoxical growth effect" in some strains, where higher levels of drugs like caspofungin
453 result in higher MIC values (124, 126).
454
455 Mutations in the mismatch repair gene *MSH2* can generate hypermutator strains with
456 increased frequency of drug resistance to triazole and echinocandin compounds (87, 121).
457 Most of the *C. albicans* and *C. glabrata* genes conferring resistance to azoles and
458 echinocandins – for example *CaERG11*, *CaERG3*, *CaTAC1*, and *CaFKS1/GSC1* in
459 *C. albicans*, as well as *CgERG11*, *CgPDR1*, *CgFKS1*, and *CgFKS2* in *C. glabrata* – can
460 be rapidly screened for by next generation sequencing and may increasingly inform clinical
461 decisions (128). However, phenotypic analysis of drug susceptibility will remain key to
462 identifying those isolates with previously unrecognized resistance mutations, those
463 acquiring multiple resistance mechanisms in a stepwise manner, and in those strains where
464 up-regulation of normal house-keeping genes causes elevated MICs. It is noted also that
465 the relevance of MICs measured *in vitro* to the *in vivo* performance of an antifungal is not
466 always clear.
467
468 Continued exposure to a range of antifungals can lead to the stepwise evolution of drug
469 resistance leading to an MDR phenotype that can also involve acquisition of resistance to
470 amphotericin B and flucytosine (129). For example, in *C. glabrata*, prolonged antifungal
471 treatment of a patient was observed to lead to the selection of mutations in *CgFUR1* and
472 *CgFKS2* along with the overexpression of *CgCDR1* and *CgCDR2* (130).
473

MOLECULAR AND CELLULAR BIOLOGY

Genome Biology

The considerable evolutionary distance between *C. glabrata* and *C. albicans* is reflected in a number of important differences in the evolution and structural organization of their genomes. *C. albicans* (but not *C. glabrata*) is one of at least eight *Candida* species that have a non-canonical CTG codon (the CTG clade). This results in the decoding of the CTG codon as serine instead of leucine. This is a fundamental difference in genome biology, reflecting the considerable evolutionary divergence between *C. glabrata* and *C. albicans*. This codon reassignment also provides practical constraints in *C. albicans* molecular genetics — for example, the expression of heterologous proteins in *C. albicans* usually requires codon correction and optimization. *C. glabrata* is a nearer phylogenetic relative to *S. cerevisiae* than to *C. albicans* and is part of a group of yeast-like species that have undergone an ancestral whole genome duplication event (WGD). The *C. glabrata* karyotype has 13 chromosomes while *C. albicans* has 8 chromosomes with a relatively compact genome that displays relatively short intergenic spacing distances compared to *C. glabrata*. As a result, the two pathogens display significant differences in gene regulation, expression, clustering and in genome stability. The ancestral WGD event has also shaped the contemporary genome architecture — for example, the 12.3 Mb haploid genome size of *C. glabrata* is only slightly smaller than the 14.3 Mb diploid *C. albicans* genome. However, the GC content, average number of genes, and average gene size is comparable in both species (33.5% vs. 38.8%, 6107 genes vs. 5283 genes, and 1468 bp vs. 1479 bp in *C. albicans* and *C. glabrata*, respectively) (1, 131, 132).

C. albicans and *C. glabrata* have remarkably plastic genomes (132). A major aspect of their extensive genomic diversity is the capacity for aneuploidy — a condition characterized by variability in chromosome number that is relevant, for example, to the evolution of drug resistance properties (see above). This phenomenon results from chromosomal mis-segregation during processes such as mating, mitosis, and the response to DNA damage due to environmental stressors. In diploid *C. albicans*, loss (monosomy) or gain of chromosomes (trisomy or tetrasomy) can occur. Quasi-stable haploid strains of *C. albicans* have been generated that have promoted new forward genetics strategies for mutant analysis (133, 134). On the other hand, haploid *C. glabrata* strains can become disomic. While loss of chromosomes in haploid and diploid cells of *C. glabrata* or *C. albicans* can potentially be lethal due to the loss of essential genes and potential fitness reduction due to mis-segregation, aneuploidy can also confer advantages under adverse and stressful conditions and may enhance *in vivo* survival (135, 136). For example, exposure to antifungals can select for aneuploidy variants that have an increased copy number of drug resistance genes (see above). Aneuploidy's roles extend beyond resistance, influencing commensal growth. Recent studies revealed that *C. albicans* can acquire an extra copy of chromosome 7, which alters the dosage of the hyphal repressor gene *NRG1*, thereby reducing filamentation and the expression of virulence genes associated with invasive growth *in vivo* (137). Aneuploidy associated with reduced virulence was reported at a high frequency during exposure of *C. albicans* to the mouse oral cavity (138). Collectively, these findings suggest that while aneuploidy might pose challenges, it can be well-tolerated and even be advantageous.

In addition to aneuploidy, the genomic landscape of *C. albicans* is also shaped by chromosomal rearrangements, insertions, deletions, point mutations, copy number variations (CNV), short tandem repeats (STRs), and loss of heterozygosity (LOH) — all of which can foster adaptability to harsh conditions (135). While STRs are prevalent in *C. albicans* and confer high mutation rates, large tandem repeats (LTRs, 65-6499 bp) contribute to CNV, LOH, and chromosomal inversions, further affecting genome structure (139). For example, oropharyngeal infections were found to be associated with an LTR event, causing trisomy of chromosome 6 and a non-virulent phenotype in *C. albicans* (138). Such tandem repeats in open reading frames are also reported to orchestrate allelic homologous recombination, notably in multigene families encoding enzymes and transporters, thereby influencing pathogenicity (140). In contrast, LOH is not relevant in the haploid *C. glabrata* genome, which also has fewer STRs, yet this organism displays greater genetic diversity within clades than *C. albicans*. Extensive CNVs and aneuploidies in *C. albicans* drive this diversity, resulting in adaptation to antifungals and changes in virulence (141, 142).

Pleomorphism and Morphogenesis

Reversible morphological transitions have been identified as important determinants of commensal and pathogenic growth of a range of fungi. Both *C. albicans* and *C. glabrata* exhibit a range of cellular and colonial morphologies (Figure 2). *C. albicans* can transit from yeasts to parallel sided, branching hyphae and conjoined elongated synchronously dividing buds called pseudohyphae. Each morphotype displays unique cell properties and

interactions with its environment. Additionally, *C. albicans* can also form enlarged yeasts called Goliath cells upon zinc starvation (143, 144) and a range of cell types associated with mating (145). A more limited number of cellular morphotypes exist for *C. glabrata*, however, emerging evidence suggests that phenotypic switching and mating could influence virulence (141, 146). Recently, some *C. glabrata* isolates have been found in stable diploid or hyperdiploid (>2N) states exhibiting different colony morphologies and variations in virulence capacity (147). Similarly, *petite* phenotypes of *C. glabrata* influence virulence and antifungal resistance (110, 112). Furthermore, an aggregating phenotype has also been recorded among *C. glabrata* clinical isolates (148). However, the mechanisms that regulate the transition between these phenotypes are yet to be elucidated.

Hyphal Growth and Tropisms

Hyphal morphogenesis is critical in *C. albicans* for invasive infiltration into human tissue and translocation from the gut into the bloodstream (149, 150). Hyphal-associated proteins mediate adhesion and invasion *via* induced endocytosis (151-153). In addition to induced endocytosis, *C. albicans* hyphae invade epithelial cells by active penetration (26). Recent microfluidic studies demonstrated that hyphal protrusive forces in the 100 MPa range allow physical penetration of host tissues. However, encounters with stiffer substrates result in Cdc42-independent alteration of cell morphology, suggesting that host cell surface stiffness influences hyphal active penetration (154, 155) and invasion of host membranes by breaching or trans-cellular tunnelling (156). One major difference in the physiology of *C. albicans* and *C. glabrata* is that *C. glabrata* does not make filamentous parallel sided branching hyphae, but it is able to form elongated, conjoined, pseudohyphae under certain conditions (29, 157). *C. albicans* hyphae display a number of behaviors and growth

responses, such as the ability to form helical shaped cells on hard surfaces and to turn and bend in relation to surface contours on the sub-stratum (thigmotropism) (158-161). These tropisms are calcium-dependent responses (160) and involve regulation of the polarisome complex of proteins in the hyphal apex that marks the site at which cell expansion takes place (159, 161). Furthermore, the Spitzenkörper, a vesicle cluster at the tip of a growing hyphae, has gained attention in recent years in relation to its role in thigmotropism (161-163). It functions synchronously with the polarisome complex to sustain hyphal elongation and directional growth (164). A recent review (165) provides valuable and most current information on effectors and influencers of hyphal growth. It is not yet known to what extent these tropisms confer an advantage to *C. albicans* in navigating through human tissues.

Phenotypic Switching

Phenotypic switching is manifest as a high frequency reversible transition between different colony types. It is not the result of mutations, but rather the consequence of regulation of silent chromatin states in key locations in the genome (166-168). Phenotypic switch variants have changes in physiology that affect virulence and a number of important physiological properties.

Phenotypic switching was first discovered in the *C. albicans* strain 3153 (166). The White-Opaque switching in the *C. albicans* WO-1 strain was subsequently found to be critical for efficient mating of strains (see below) (169, 170). The more bean-shaped opaque phase yeast cells were found to be the mating-competent switch variant (171). Switch variants

585 also confer other properties relevant to the organism's pathology. For example, opaque
586 cells are dominant colonizers of the skin, mediated by the secreted aspartic protease Sap1
587 (172), and to a lesser extent of the heart and the spleen (173, 174). However, in the
588 mammalian gastro-intestinal (GI) tract, *C. albicans* white cells can also switch to a Wor1-
589 regulated commensal cell type known as the GUT (Gastrointestinally-indUced Transition)
590 phenotype. GUT cells are distinct from opaque cells and express a transcriptome optimized
591 for the GI tract (175). To add to its phenotypic versatility, *C. albicans* also displays a "gray"
592 phenotype in a tristable white-gray-opaque switching system. Gray cells differ from white
593 and opaque cells in appearance, mating competency, expression of secreted aspartic
594 proteases, and virulence (176). In addition, white cells are preferentially phagocytosed over
595 opaque phase cells suggesting opaque phase cells may be better able to escape immune
596 clearance (177). Efg1 and Wor1 are established key regulators of phenotypic switching in
597 *C. albicans*. More recently, the Cph1 transcription factor was also implicated in phenotypic
598 transition and white cell pheromone response (178). Besides gene expression, gene dosage
599 is also crucial for white-opaque switching, as *EFG1* hemizygosity is important for
600 transition to opaque cells and, subsequently, mating. It is therefore not surprising that
601 clinical isolates are often found to have undergone a loss of one functional *EFG1* allele *via*
602 *de novo* mutation or gene conversion events, particularly in the GI tract (179). However, a
603 recent study reported a Wor1-independent opaque phenotype, suggesting the presence of
604 alternate as-yet unidentified opaque cell regulatory pathways (180). Although some
605 *C. albicans* phenotypes are extensively studied, limited information is available on the
606 nature of the variability exhibited by other colony phenotypes of *C. albicans*. For example,
607 the regulatory pathways and cellular features of the originally described smooth, star,

608 irregular-wrinkled, ring, stipple, fuzzy, and revertant and smooth colonies of strain 3513A
609 (181) remain largely unknown. *C. glabrata* can also exhibit colonial phenotypic switching
610 forming white, light brown, dark brown, and very dark brown colonies that can be
611 distinguished by graded colony coloration on $CuSO_4$-containing agar. These four
612 phenotypes form the core switching system and differ in their expression of MT-II, a
613 metallothionein gene. *C. glabrata* can also form irregular-wrinkled colonies (182).
614 Although some regulatory mechanisms may remain elusive, various studies have
615 demonstrated that spontaneous phenotypic transitions are crucial for mating, virulence,
616 immune evasion, and adaptation to a range of host environments.

617 **Mating**

618 The recognition of a parasexual cycle as a part of both *C. albicans* and *C. glabrata* life
619 cycle has expanded our understanding of *Candida* spp. phenotypes (146, 183). Mating in
620 *C. albicans* results in formation of irregular tubular mating projections called “shmoos”
621 (184, 185). Opaque phase cells of *C. albicans* that carry both MTLa and MTLα alleles are
622 greatly increased in mating competence. A few clinical isolates have been identified that
623 are MTL-homozygous (a/a or α/α) and facilitate *WOR1*-mediated white-to-opaque
624 switching to allow mating between a/a and α/α cells (135, 186, 187). Same-sex mating
625 between MTLa cells regulated by the Hsf1-Hsp90 pathway has also been identified (188).
626 Both homothallic (same-sex) and heterothallic (between opposite mating types) mating
627 have been described, with unisexual mating occurring in mutants lacking the Bar1 protease
628 that enables autocrine pheromone signaling (187). Additionally, *C. albicans* can also
629 undergo switching-independent sexual mating under certain environmental conditions
630 including glucose starvation (169, 189). Although the pathways and functions of the sex

genes involved are yet to be elucidated, glucose depletion can result in overexpression of pheromone-sensing and mating-associated genes, and a decreased expression of mating repressor genes. A full sexual cycle for *C. albicans* has yet to be described, even though most of the genes required for meiosis are known to be present in the genome.

In contrast to *C. albicans, C. glabrata* is a haploid fungus and contains three mating-type loci – *MTL1* (containing a or α information), *MTL2* (containing information for a) and *MTL3* (containing information for α). MTL 1 and 2 are transcriptionally active while *MTL3* is subject to subtelomeric silencing (190). In this regard, *C. glabrata* has adopted a 'fluid' MTL identity and can switch its mating type to allow (para)sexual mating (146). At this stage it is not clear whether *C. glabrata* can execute all the steps required to complete a full sexual cycle. Phenotypic switching does not seem to be relevant to the mating cycle.

Morphogenesis and Biofilms

Regulation of the yeast-to-hypha transition in *C. albicans* has been studied extensively and is not covered here in detail because it has been frequently reviewed (143, 191-195) and is not relevant to *C. glabrata* physiology (131). However, the transcriptional machinery that orchestrates morphological transitions involve multiple positive and negative regulatory factors (e.g., Cek1-MAPK, Ras-cAMP, Hog1-MAPK, Tor1 pathways), some of which also affect other aspects of physiology – such as biofilm formation. Biofilms of *C. albicans* commonly constitute a profusion of hyphae emanating from a basal layer of yeast cells that colonize a surface. *BCR1*, *EFG1*, *NDT80*, *ROB1*, *TEC1*, *BRG1*, *FLO8*, *GAL4*, and *RFX2* (196) all play a role in *C. albicans* biofilms, and *TEC1* and *STE12* are important for biofilm

formation of *C. glabrata* (197). For successful morphological transitions these transcriptional circuits rely on co-ordination with chromatin and histone modifier and remodeling complexes (198). For example, the *C. albicans* SWI/SNF and RSC (Remodels the Structure of Chromatin) complexes and histone deacetylase Sir2 are known to regulate filamentation (199, 200), and by extension influence biofilm formation.

C. albicans and *C. glabrata* both are capable of forming single or mixed-species biofilm communities in which the fungal cells are encased in an extracellular matrix (ECM). This can result in poor penetration of antifungal drugs, encourage antifungal resistance, and also provide protection from immune phagocytes (201). Biofilm formation hinges on the adhesion capacity of the component cells. In *C. albicans*, the Als family of proteins, especially the hyphal associated proteins Als3, and Hwp1 aid adhesion (32, 153, 202), while Epa proteins serve this role in *C. glabrata* (203). Many secreted biofilm components of *C. albicans*, including almost half of all biofilm proteins, are delivered *via* extracellular vesicles (EVs), and inhibition of EV secretion increases the sensitivity of biofilm cells to fluconazole (204). It is not yet known whether EVs contribute to biofilm formation in *C. glabrata*. Hyphal associated Sap proteases are required for proper *C. albicans* biofilm development *in vitro* and *in vivo* (205). While both species form biofilms *in vivo*, they exhibit stark differences in biofilm structure and composition. *C. albicans* biofilms typically include a proliferation of filamentous hyphae, whereas *C. glabrata* biofilms consist of yeast cells with occasional pseudohyphae-like structures reported *in vitro* (29, 182). Other studies suggest that both species can also form biofilms in which mating takes place (146, 206, 207). In *C. albicans*, white cells were found to secrete pheromones and

create a favorable environment for a small population of opaque cells to mate (208). Furthermore, they can also form mixed-species biofilms with bacteria like *Staphylococcus* and *Streptococcus* (209-211). On medical devices, teeth, and other host surfaces, specific biofilms can be formed of unique composition and function, which can alter the host microbiome. These studies collectively demonstrate the phenotypic diversity of *Candida* spp. biofilms, highlighting their complex nature and the challenges they pose.

Cell Wall

The *Candida* spp. cell wall is a multifunctional organelle and plays a crucial role in physiological processes such as morphogenesis, adherence, biofilm formation, immune recognition and evasion, and antifungal drug targeting (212). It is a complex multi-layered structure with a chitin- and β-(1,3)- and β-(1,6)-glucans-rich inner layer, and an outer layer composed mainly of highly mannosylated glycoproteins. The cell wall proteins are mostly GlycosylPhosphatidylInositol (GPI)-anchored *via* a C-terminal ω-site to β-(1,6)-glucan and thereby to the β-(1,3)-glucan inner skeleton. Whilst the general arrangement of the major polysaccharides in the cell walls of *C. albicans* and *C. glabrata* is similar, significant differences exist in the cell wall proteome. Approximately 100 cell wall proteins like adhesins, Saps (*C. albicans*), yapsins (*C. glabrata*) and other hydrolases, transglycosidases, deacetylases, and amyloid forming proteins are encoded in the genomes of *C. albicans* and *C. glabrata*, of which 10-15 are dominant under any set of environmental conditions (213, 214). A novel class of cell wall proteins with β-helix folds were recently identified in *C. glabrata* that mediate adhesion in clinical isolates (215). The cell wall can undergo dynamic modifications during morphogenesis and in response to environmental changes. For example, exposure to an echinocandin compromises β-(1,3)-

699 glucan structure, resulting in overproduction of chitin and anchoring of many GPI-proteins
700 to chitin (123, 212, 213). These cell wall compensatory reactions are controlled by multiple
701 signaling pathways including the MKC, HOG, and calcineurin pathways and a subset of
702 bespoke transcription factors including Rlm1, Sko1, Crz1, and Cas5 (206). The calcineurin
703 pathway was recently found to regulate the cell wall integrity signaling pathway in
704 *C. albicans*. It modifies chitin synthesis under echinocandin stress and ensures that chitin
705 levels are maintained within fixed boundaries to prevent the wall from becoming too rigid
706 (123). Additionally, transcription factors such as Sfp1 and Czf1 have also been implicated
707 in maintaining cell wall integrity under different environmental conditions (216, 217).
708 Recent reviews (218, 219) provide a comprehensive overview of the cell wall proteome of
709 *C. albicans* and the diversity of GPI-anchored proteins in fungi, respectively. The role of
710 specific cell wall proteins in commensalism and diseases is discussed below.

711

INTERACTION BIOLOGY

712 **Immune Recognition**

713 The first step in mounting a protective immune response to *Candida* species is the sensing
714 of the fungus *via* receptors on host immune cells *via* recognition of components of
715 pathogens with conserved molecular patterns – termed pathogen-associated molecular
716 patterns (PAMPs). These PAMPs are predominantly fungal cell wall and intracellular
717 components, such as nucleic acids. Cells of the innate immune system recognize these
718 PAMPs directly through membrane-bound and cytoplasmic pattern recognition receptors
719 (PRRs), or indirectly through pre-opsonisation *via* complement or antibodies. PRRs can be

subdivided in several families, including C-type lectin receptors (CLRs), Toll-like receptors (TLRs), NOD-like receptors (NLRs), and RIG -like receptors (RLRs), which differential expression on various (non-) immune cells leads to tailored activation of protective immune responses (220-222) (Figure 3). It should be noted that most studies to date of the role of specific PRRs have been carried out only with *C. albicans*. In addition, limitations in the utility of the mouse model for *C. glabrata* virulence studies has compromised the ability to assess the consequences of knock-out mutations in the host or fungus on pathogenicity.

CLRs, alone (e.g., Dectin-1) or *via* association with Fc receptor γ chain (e.g., Dectin-2, Mincle, Dectin-3), signal through the Syk/PKCδ/CARD9/Bcl-10/MALT1 or RAF1 pathways. Caspase recruitment domain-containing protein 9 (CARD9) is crucial, as humans and mice with defective CARD9 signaling are more susceptible to invasive *Candida* spp. infections (223-227). *Candida* spp. mannans and mannoproteins are recognized by several CLRs including: Dectin-2, Dectin-3, Mincle, Mannose receptor, and DC-SIGN. Dectin-2 recognizes high mannose structures (228, 229), and absence of the receptor reduces innate immune cell recruitment and activation, phagocytosis, NETosis, and induction of Th17 cell responses, rendering mice more susceptible to systemic *C. albicans* and *C. glabrata* infection (230-235). In heterodimeric combination with Dectin-2, Dectin-3 recognizes α-mannans, and mice deficient for Dectin-3 are also susceptible to *C. albicans* infection (236). Recognition of *N*-linked mannans (229, 237) by Mannose receptor induces phagocytosis of *C. albicans* (238) and production of various pro-inflammatory cytokines (239-241), but is not required for survival in a systemic

C. albicans murine infection model (242). DC-SIGN (and murine homolog SIGNR1) also interacts with *N*-linked mannan (229, 243, 244), and recognition leads to phagocytosis, cytokine and ROS production, and modulation of TLR signaling *via* a Raf-1 dependent pathway (245-249). Mincle binds *C. albicans* steryl mannosides (250, 251) and is involved in modulation of phagocytosis and killing, cytokine responses, and control of kidney fungal burdens (233, 234, 252-254). *Candida* spp. β-1,3-glucan is recognized by Dectin-1 (255) and mediates phagocytosis, generation of inflammatory cytokines, chemokines and ROS, and Th17 cell differentiation (227, 256). Absence of Dectin-1 in mice was found to be associated with increased mortality, higher fungal burden, and reduced inflammatory cell recruitment after *C. albicans* or *C. glabrata* systemic infection (234, 256-258). However, it was noted that the susceptibility of Dectin-1 deficient mice to *C. albicans* was dependent on the levels of chitin content of the fungal cell wall (127). In humans, a single nucleotide polymorphism (SNPs) in *CLEC7A* (Dectin-1), which affects inflammatory cytokines in response to *C. albicans*, results in the absence of Dectin-1 from host myeloid cells and increases susceptibility to chronic mucocutaneous candidiasis (259), *Candida* spp. colonization (260), and recurrent vulvovaginal candidiasis (261).

TLRs recognize *Candida* spp. *via* extracellular leucine-rich repeat regions, and signal *via* an intracellular TIR homology domain leading to the activation of MyD88 or TRIF-dependent pathways. The importance of TLR interaction in *Candida* spp. recognition is evident from studies using mice that lack MyD88. These animals show increased mortality, fungal burden, and decreased pro-inflammatory cytokine production in systemic *C. albicans* infections (262). However, humans with *MyD88* or *IRAK* mutations do not

present with increased or exaggerated fungal infections (263, 264). TLR2 can form heterodimers in combination with TLR1 and TLR6, and the heterodimeric complex recognizes phospholipomannan (265) and chitin (266, 267), inducing pro- and anti-inflammatory cytokine responses and differentiation of haematopoietic stem cells and T-cells (265, 267-271). Mice deficient for TLR2 exhibit increased *C. albicans* colonization of the gastrointestinal (272) and vaginal tracts (273), whereas in systemic infection both increased and decreased susceptibility have been reported in a TLR2-deficient background (268, 271). Absence of either TLR1 or TLR6 results in a normal susceptibility in systemic models of *C. albicans* infection (274). In humans, SNPs in TLR1 and TLR2 have been associated with increased susceptibility to candidemia (275) and recurrent vulvovaginal candidiasis (261), respectively. *Candida* spp. *O*-linked mannan (237, 276) recognition by TLR4 induces pro-inflammatory cytokine responses, phagocytosis, and recruitment of immune cells (277-279). Opposing consequences have been described in models for systemic models of *C. albicans* infection, with TLR4-deficient mice being more susceptible than (277), or not different to (280) wildtype mice. Recognition of *Candida* spp. DNA by TLR9 induces pro-inflammatory cytokine responses, and absence of the receptor in systemic models of *C. albicans* infections increased mortality in one study (281) – but showed no effect in another (282). TLR3 and TLR7 both recognize RNA, and while a SNP in *TLR3* showed decreased IFNγ responses to *C. albicans* and increased susceptibility to cutaneous candidiasis (283), mice lacking TLR7 were more susceptible to systemic *C. albicans* infection (281).

NLRs are intracellular receptors containing leucine-rich repeats, NACHT, CARD or PYRIN domains. NOD2 and the inflammasome-activating receptors NLPR3, NLRP10, and NLRC4 are involved in recognition of *Candida* species. *C. albicans* chitin induces IL-10 cytokine responses *via* NOD2 (266), whereas a SNP in *NOD2* had no effect on *C. albicans*-stimulated PBMCs cytokine responses, nor was an association with disease in patients with *Candida* spp. infections observed (284). The NLRP3 inflammasome is activated more strongly by *C. albicans* hyphae than yeast cells (285). NLRP3 recognition of *C. albicans* β-glucans, secreted aspartic proteases (Saps) or candidalysin activates caspase-1, or caspase-11, for processing of pro-IL-1β and pro-IL-18 into their biologically active forms (286-289), induces Th17 responses (Cheng 2011), but can also trigger a programmed cell death pathway (pyroptosis) facilitating fungal escape from inside macrophages (290, 291). Mice defective for components of the NLRP3 inflammasome are more susceptible to disseminated *C. albicans* infection (292-294). In humans, a polymorphism and variable number tandem repeat in the *NLRP3* gene are associated with recurrent vulvovaginal candidiasis and decreased IL-1β production in response to *C. albicans* (295, 296). NLRP3-independent caspase-8 activation by *C. albicans* β-glucans has also been shown to induce processing of pro-IL-1β and pyroptosis (297, 298). Other inflammasomes, NLRP10 and NLRC4, play a protective role in systemic (299) and mucosal candidiasis (300), respectively, and NLCR4 also regulates NLRP3 inflammasome activity during *Candida* spp. infection (301).

Other PRRs involved in *Candida* spp. recognition include Galectin-3 (302, 303), Langerin (247, 304), collectins (MBL, SP-A, SP-D) (305-307), EphA2 (308, 309), EphB2 (310),

CR3 (CD18/CD11b) (311), CD14 (276), CD23 (312), CDw17 (313), LYSMD3 (314), SCARF1 and CD36 (315), NKp46 (316), and MDA5 (317).

Recognition of PAMPs by PRRs leads to activation of innate and adaptive immune responses and effector mechanisms to clear the invading fungus (Figure 4). Epithelial cells form a physical barrier with the environment and respond to the presence of *C. albicans* with activation of NF-κB and a biphasic MAPK response (318, 319). Initially, NF-κB and the MAPK c-Jun are activated, independent of cell morphology. Subsequently, a second MAPK phase consists of MKP1 and c-Fos activation *via* EGFR signalling (36, 320) in presence of hyphae and the secreted cytolytic pore forming peptide, candidalysin. Activation induces secretion of antimicrobial peptides such as cathelicidin (LL-37) and β-defensins, with direct antifungal activity (321-325), and of cytokines, chemokines, and alarmins, resulting in recruitment and activation of innate immune cells, e.g. neutrophils, monocytes, macrophages, and dendritic cells (318, 319). These professional phagocytes are crucial for uptake and killing of *C. albicans* and *C. glabrata*, and absence of these cells has been associated with increased susceptibility to infection in animal models and in human disease (326-329). Uptake of non-opsonized *Candida* spp. is initiated by phagocytic PRRs (e.g., Dectin-1, Mannose Receptor, DC-SIGN, Dectin-2, and Mincle), whereas recognition by CR3 and Fc receptors is important for pre-opsonized *Candida* spp. (233, 240, 245, 311, 330). *C. albicans* hyphae are potentially problematic for phagocytic cells to take up (331), however, longer hypha can be folded in order to be engulfed into the phagosome (332). After engulfment, the phagosome undergoes multiple fusion events with endo- and lysosomes to generate an increasingly hostile environment with high acidity, and

834 oxidative and non-oxidative mechanisms to kill *Candida* species. Phagocytes produce
835 reactive oxygen species (ROS) through the NADPH oxidase complex and
836 myeloperoxidase, while reactive nitrogen species are formed by inducible nitric oxide
837 synthase (iNOS). Absence of these enzymes has been associated with increased
838 susceptibility to systemic candidiasis in animal models (333, 334), yet *in vitro* ROS- and
839 NOS-deficient macrophages were not affected in their capacity to kill *C. albicans*,
840 indicating compensatory roles for other mechanisms (334). These non-oxidative
841 mechanisms include the induction of hydrolases (e.g. lysozyme and chitinases (335, 336)
842 and antimicrobial peptide formation [defensins, cathelicidins, and histatins] (321-325))
843 with direct anti-*Candida* spp. activity. Indirect mechanisms such as the restriction of
844 essential nutrients such as metals by calprotectin also contribute to protection (337). In
845 addition to phagocytosis, neutrophils can undergo NETosis, a process of programmed cell
846 death resulting in neutrophil extracellular trap (NET) formation, which consist of a web of
847 DNA and histones, loaded with proteins with antifungal activity (337-339). Other innate-
848 like cells implicated in the anti-*Candida* spp. immune response include natural killer cells
849 (NK cells) (340, 341), innate-like lymphocytes (ILCs) (342-344), invariant NK T-cells
850 (345), γδT cells, and natural Th17 cells (346).
851
852 Dendritic cells (DCs) not only phagocytose and kill *Candida* spp., but also link innate to
853 adaptive immunity. Activation of DCs induces upregulation of major histocompatibility
854 complex I & II molecules for the presentation of fungal antigens, and it enhances
855 expression of co-stimulatory molecules and release of cytokines and chemokines which
856 drive $CD4^+$ T-cell responses. Th17 cells, characterized by the production of IL-17 and IL-

22, play a pivotal role in anti-*Candida* spp. immunity. IL-17 promotes neutrophil trafficking and fungicidal activity (347, 348), whereas IL-22 is important for barrier integrity of the epithelium and induction of antimicrobial peptides (349). In mice, deficiency in the IL-17/IL-17R axis and its signaling components is associated with increased susceptibility to mucosal (350, 351), skin (352), and systemic candidiasis (348). Similarly, humans with impairments in Th17 development and IL-17-dependent signaling *via* mutations in RORC, IL-17RA, IL-17F, ACT1, CARD9, STAT1 or STAT3 show increased development of chronic mucocutaneous candidiasis (223, 353-357). Th1 cells, characterized by the production of IFNγ, are important for phagocyte maturation and killing of *Candida* spp. Mice deficient for IL-18, which drives Th1 responses, are more susceptible to disseminated *C. albicans* infection (358), whereas its supplementation enhances host resistance (359). Similarly, IFNγ immunotherapy has shown to improve outcome in humans and mice with systemic candidiasis (360, 361). In contrast, Th2 and T regulatory cell subsets are considered detrimental in *Candida* spp. infections. Augmented Th2 differentiation in GATA-3-overexpressing mice was associated with increased susceptibility to *C. albicans* infection (362), whereas blocking IL-4 resulted in increased resistance (363). Tregs were shown to enhance Th17 cell induction, driving pathology (351), and mice deficient for IL-10 were more resistant to systemic candidiasis (363, 364). B-cells are characterized by their production of antibodies, but they also phagocytose and present antigens and produce cytokines and chemokines. Their role in the protection against *Candida* spp. infections is suggested to be modest, as mice lacking B-cells were largely unaltered in their susceptibility to *C. albicans* infection (365-367). However, antibody-independent B-cell responses (368, 369) and exogenous supplementation of

antibodies directed against *Candida* spp. have been shown to be beneficial in the immune response (see below).

Commensal Interactions with the Host

While the pathogenicity of *Candida* spp., in particular *C. albicans*, has been well investigated (370), the commensal lifestyle of these species has only recently come into focus (371-375). Both *C. albicans* and *C. glabrata* normally exist as commensals on mucosal surfaces of the human body, and they can frequently be found in the gut, oral or vaginal cavities (376). However, the commensal lifestyle of *C. glabrata* is not well investigated so far, and further research is needed to better understand the mechanisms and traits that promote the commensal stage of *C. glabrata*. Most humans in westernized countries are temporarily or stably colonized by *C. albicans* (376-378). The ability of *C. albicans* to grow in different morphologies does not only play a central role in pathogenicity, but also seems to be crucial for the commensal colonization of mucosal niches. Until recently, the general consensus was that yeast cells are the predominant form in experimental commensalism in mice (379). However, hypha-associated genes are highly expressed during gut colonization (380, 381) and more recent studies have shown that hyphae are also present during gut colonization in mice (382). The presence of yeast or hyphal cells during commensalism likely depends on the microbiome or the localization in the gut (382). However, the intact murine bacterial microbiota of many mouse strains resists the ability of *C. albicans* to colonize the gut (383, 384), which has led to colonization models based on antibiotic treatments. Therefore, data obtained from traditional commensal models with antibiotic-treated mice lack the influence of an intact microbiome that may be important for the maintenance of commensalism.

Microevolution experiments in a murine model based on antibiotic treatment led to the selection of *C. albicans* mutants that had lost their ability to form hyphae (385). Targeted mutants that lack transcriptional regulators of hyphae formation are generally defective in virulence but are often better colonizers of the murine gut than the wild type in mouse models based on antibiotic treatment, but also in gnotobiotic mice (175, 382, 386). The ability to colonize is, however, not necessarily linked to the morphology *per se*, but seems to be determined by morphology-specific transcriptional programs. A deletion mutant of *UME6*, coding for a regulator of filamentation under *in vitro* conditions, colonized better than the wild type, but surprisingly still formed hyphae, similar to the wild type, in the murine gut. Its increased ability to colonize mainly stemmed from its lack of expression of the immunogenic secreted aspartic proteinase Sap6 (382). Additionally, overexpressing *CRZ2*, a filamentation regulator gene (387), enhanced early colonization in a mouse colonization model (388). Another regulator of hyphal morphogenesis, *EFG1*, has also been found to be crucial for commensalism, and its expression relies on the host's immune status (389). Efficient colonization therefore seems to require the downregulation of virulence-associated transcription programs in *C. albicans*.

The gut is generally an iron-rich environment, but its changing abundance can affect the composition of the gut microbiota (390). In order for *C. albicans* to survive and proliferate under these conditions, it has to regulate its iron acquisition mechanisms. During commensal growth, *C. albicans* downregulates iron uptake genes through the expression of *SFU1*, a gene encoding a GATA family transcription factor. Sfu1 inhibits *SEF1*

926 expression, which codes for a global regulator of iron uptake (391). *C. albicans* also has
927 different ferroxidases of different affinities, which were found to have distinct roles in
928 different murine GI niches with different iron availability (392). Moreover, other
929 metabolites such as bile acids can also contribute to the commensal status of the fungus
930 (393, 394). Other factors that affect commensalism of *C. albicans* include the host's diet
931 (372, 395) and the physiological conditions of the gut, such as hypoxia (396). Additionally,
932 through the expression of *WOR1*, *C. albicans* cells can be transformed to the commensal-
933 specific GUT cell type (175). GUT cells downregulate iron uptake-related genes to prevent
934 iron-mediated toxicity (175), and they have a distinct metabolic profile that promotes
935 commensalism in the lower GI tract. In this short-fatty acids-enriched environment, they
936 benefit from the upregulation of fatty acid catabolism, and they also upregulate catabolism
937 of *N*-acetylglucosamine, which is beneficial for commensalism (397). Paralleling the
938 findings of the transcription factor mutants, they also downregulate several other genes
939 with functions in virulence (175). No colonization-specific cell types have so far been
940 reported for *C. glabrata*. However, a remodeling of *C. glabrata*'s cell wall, specifically the
941 increase of chitin and β-mannans, has been described during colonization in a murine
942 model of induced acute colitis (398).
943
944 A possible explanation for the two different lifestyles of *C. albicans* as a commensal and
945 pathogen, could be that these lifestyles are associated with different strains (382, 399).
946 However, a recent study found that commensal isolates from humans retained their ability
947 to cause infection in an invertebrate model, and that these isolates are competent to cause
948 infection of humans (400). In fact, phenotypic differences among major *C. albicans* strain

clades are minor (401). It seems clear that host factors (402, 403) and antagonistic bacteria of the microbiome (404, 405) (see below) are involved in maintaining *C. albicans* in the commensal phase. However, future research may help to understand the molecular and environmental factors that promote commensal or virulent attributes, and this may open new avenues for suppressing virulence. Because *C. albicans* cells are predominantly commensal in nature, it is likely that strains are positively adapted for this lifestyle. However, almost all commensal strains have the potential to cause diseases. Thus, the fungus must be exposed to conditions which can "train" the fungus for both commensalism and pathogenicity, a concept that has been proposed as the "commensal virulence school" (406). Antivirulence/avirulence traits in pathogenic fungi and their potential as therapeutic targets have been reviewed extensively in (407) and (408).

Interactions with Bacteria

During their commensal state, *Candida* spp. constantly interact with many species of bacteria and fungi of the microbiome. These interactions contribute to maintaining *Candida* spp. commensalism and inhibiting the transition to an infectious state (409, 410). *Staphylococcus aureus* is a facultative anaerobic bacterium that colonizes the skin and mucosae. In biofilms *S. aureus* synergizes with *C. albicans*, and both microbes increase each other's infectious potential and drug resistance (411). Recent reports suggest that *S. aureus* can inhibit *C. albicans*' transition to the hyphal form and limits its pathogenicity *via* its toxin, alpha-hemolysin (412). In contrast, *S. aureus* culture supernatants can induce *C. glabrata* cell death (413). Cruz and colleagues found that the Gram-positive bacterium, *Enterococcus faecalis*, and *C. albicans* impair each other's virulence in a *C. elegans* model. *E. faecalis* excretes a peptide, EntV, that reduces fungal filamentation and virulence

(414). Medium conditioned by the growth of the Gram-positive *Clostridioides difficile* can inhibit hyphal growth, and p-Cresol, a product of the bacterium's tyrosine metabolism, even promotes the hypha-to-yeast transition in *C. albicans*. Interestingly, in the presence of *C. albicans, C. difficile* is able to grow in aerobic conditions, which are normally toxic for the bacterium (415). The interactions of *Candida* species with *Pseudomonas aeruginosa* are similarly complex: *C. albicans* inhibits the bacterial virulence during mice colonization *via* inhibition of pyochelin and pyoverdine expression (416), and conversely *P. aeruginosa* inhibits *in vitro* formation of *C. albicans* and *C. glabrata* biofilms (417). Interestingly, *P. aeruginosa* specifically kills hyphae through contact-mediated and soluble factors, but it does not affect yeast cells (418). Indirect interactions *via* the host can also play a role: Clostridial Firmicutes and Bacteroidetes decrease *C. albicans* colonization by inducing the expression of hypoxia-inducible factor-1α (HIF-1α) in mice, which then leads to the production of the antimicrobial peptide LL-37 (383).

A well-investigated interaction is that between *Lactobacillus* and *Candida* species. Lactobacilli protect against vaginal infections by *Candida* spp. mainly through the production of lactic acid, which acidifies the vaginal mucosa (419), resulting in enhanced recruitment of neutrophils and cytokine production (420). In an *in vitro* model, *Lactobacillus rhamnosus* not only reduced hyphal elongation, but also triggered shedding of epithelial cells that helped to remove hyphae from the epithelial surface and reduced damage (405). *C. glabrata*'s stress-induced MAP kinase, Hog1, is phosphorylated at lactic acid concentrations that are produced by lactobacilli. By upregulating stress-responsive

genes, it allows growth under these conditions and thereby contributes to *C. glabrata*'s co-colonization with different *Lactobacillus* spp. (421).

Candida spp., the gut microbiota, and the host also interact metabolically with each other. *L. rhamnosus* has been found to remove carbon, nitrogen, and phosphorus sources, forcing *C. albicans* metabolic adaptations that compromise pathogenicity (404). Dietary tryptophan is metabolized by *Lactobacillus* spp. in the gut to indole-3-aldehyde, which, *via* the host aryl hydrocarbon receptor, leads to IL-22 expression. This IL-22 response promotes resistance against *C. albicans* colonization and protects the mucosal surface from inflammation (422). In an example for direct metabolic interaction, another study has shown that exposing *C. albicans* cells to gut metabolome components, specifically metabolites from *Bacteroides ovatus*, *Roseburia faecis*, and *Roseburia intestinalis*, leads to reduced expression of hypha-associated genes such as *ECE1*, *ALS3*, and *HWP1* and a reduction in epithelial damage (423). The microbiota can also affect *C. albicans* colonization and growth through the production of short chain fatty acids (SCFAs). Acetate, butyrate, and propionate have been found to inhibit germ tube and hypha formation and inhibit colonization in mice (383, 424, 425). Butyrate has the most potent effect and is produced by bacteria belonging to Firmicutes (incl. *Clostridium* spp.) and Bacteroides (426). One study showed that SCFAs lead to increased exposure of fungal β-glucan in the large intestine, which enhances immune recognition of the fungi, leading to decreased colonization in the gut of antibiotic-treated mice (427). While *C. albicans*' interactions with other microbes and the effects of them have been well studied in both *in*

vitro and *in vivo* models, the investigations into these relationships are much less developed for *C. glabrata*.

A recent discovery demonstrated that *Serratia marcescens* can predate on *Candida* spp. cells by injecting novel antifungal effectors into the cytoplasm *via* the bacterial syringe-like Type VI Secretion System (T6SS) (428). This discovery has expanded the understanding of polymicrobial competitions and is likely to have a broad relevance in *Candida* spp. biology (429). The T6SS is a complex bacterial contractile system found in numerous Gram-negative bacteria that delivers toxic effector proteins into adjacent cells or its extracellular environment (430). *S. marcescens* delivers at least two fungal-specific T6SS effector proteins, Tfe1 and Tfe2. Tfe1 triggers plasma membrane depolarization, and Tfe2 disrupts nutrient uptake and induces autophagy resulting in fungal cell death (428). Subsequently, *Acinetobacter baumannii* has also been found to possess a T6SS, with the TafE antifungal effector protein possessing DNase activity (431).

Early studies on T6SS identified an intriguing anomaly. Certain bacteria such as actinobacteria, cyanobacteria, and some species of proteobacteria were found to possess T6SS that housed a Het-C domain, which in filamentous fungi is important for regulating self/non-self-recognition. The presence of this domain in bacterial T6SS may suggest a role in fungal recognition (432, 433). Because bacteria and fungi coexist in polymicrobial communities, it is possible that antifungal T6SSs are of widespread importance in shaping the mycobiome. Recent reviews provide a more comprehensive and detailed overview of

the interactions between *Candida* spp. and bacteria in health and disease in the GI tract and on other mucosal surfaces (409, 410, 434).

Interactions Leading to Pathogenicity

Under normal physiological conditions, *Candida* spp. remain commensals with little evidence of local pathogenesis. Environmental changes such as a shift in the microbial community, disruption of the host's mucosal surface or weakening of the immune system can result in superficial or systemic infections. *Candida* spp. have multiple tools at their disposal to effectively infect the host, including adhesion and invasion, damage of the host tissue, immune invasion, and metabolic and nutritional interactions with the host cells (13, 370, 435-437).

Adhesion, Invasion, and Damage

The first step in a successful infection is the adherence to host cells. Both *C. albicans* and *C. glabrata* are equipped with adhesins that allow them to attach to host cells and form biofilms. The best-known family of *C. albicans'* adhesins is the Agglutinin-Like Sequences (Als) family, which includes Als1-Als7 and Als9. Especially Als3 is one of the most important and well-studied adhesins. Als3 is expressed during filamentation (438), and its deletion significantly reduces adhesion to epithelial cells (43). Recently, a study found that Als3 and an enolase interact with each other and allow binding to host plasma proteins (439). Another important hypha-associated adhesin is the hyphal wall protein 1, Hwp1 (202). A null mutant had reduced adherence to epithelial cells *in vitro* (202) and reduced virulence in an *in vivo* model (440). *C. glabrata* is similarly equipped with a large repertoire of adhesins, and they are considered to be among its most important

pathogenicity traits (441). Its main family of adhesins is the Epa family, which contains at least 17-23 genes depending on the strain (442). Epa1 seems to be mainly responsible for adherence to epithelial cells (442), while other proteins of the family are required for adherence to other cell types, like macrophages and endothelial cells. The *C. glabrata*-specific GPI-anchored proteins Pwp7 and Aed1 have been described as adhesins required for attachment to umbilical vein endothelial cells *in vitro* (443). The adhesins of both fungi are also associated with biofilm formation (see above). A *C. albicans* knockout of Hwp1 results in thin biofilms, and in an *in vitro* catheter model the mutant was not able to form biofilms (444). Similarly, strains with a higher expression level of *ALS3* show a higher biofilm formation rate (445), and an *ALS3* deletion mutant is deficient in producing biofilms *in vitro* (446). The *C. glabrata* Awp adhesin family is also involved in biofilm formation, together with Epa6 (30, 441).

After adhesion to their surface, the *Candida* spp. cells need to invade the cells to establish an infection. *C. albicans* invades host cells *via* two different routes: a) induced endocytosis or b) active penetration *via* the formation of hyphae. In addition to its function as an adhesin, Als3 can act also as an invasin and induce endocytosis of the fungus by normally non-phagocytic cells. Als3 as well as Ssa1, another invasin, interact with E- and N-cadherins of epithelial and endothelial cells, respectively, to induce endocytosis (447). Als3 can also interact with the heat shock protein gp96 to invade brain endothelial cells (448) and with EphA2 and EGFR to invade oral epithelial cells (449). In a recent paper, it was further shown that E-cadherin is necessary for *C. albicans* to activate c-Met and EGFR to and lead to endocytosis in oral epithelial cells (450). However, active penetration seems

to be the most common and important mechanism of cellular invasion of *C. albicans*. *C. albicans* forms hyphae, which can penetrate the host cell membrane. During this process, the fungus excretes a number of hydrolases (proteinases, phospholipases, and lipases) and other factors that may aid in tissue invasion (43). The secreted aspartic proteinase family (Saps) comprises ten members (Sap1-Sap10) and is probably the best studied among these hydrolases (451, 452). In addition, *C. albicans* possesses a hypha-associated toxin called candidalysin, the first (ribosomal) peptide toxin identified in any human fungal pathogen (36, 37, 453). Candidalysin forms pore-like structures in the membrane of host cells resulting in membrane damage (36, 454). Moderate membrane damage levels can be repaired by epithelial cells (455, 456), but sustained levels of damage lead to a series of event that are critical for *C. albicans* mucosal and systemic infections (457, 458). For example, candidalysin-induced damage activates danger-response and damage protection pathways in host cells (36, 318) (see above) and leads to activation of the epidermal growth factor receptor in epithelial cells and the NLRP3 inflammasome in macrophages (287, 320). It also drives neutrophil recruitment and immunopathology during vaginal infections (459), triggers Type 17 immunity during oral infections (460), and is essential for successful translocation of the fungus through the epithelial barrier (461). In contrast, *C. glabrata* is not known to produce any toxins.

C. albicans translocates through the epithelial barrier to reach the bloodstream for a disseminated infection. There is proof that translocation occurs through a transcellular route which involves the formation of hyphae (26). Other translocation strategies such as paracellular translocation through the epithelia barrier, and translocation through microfold cells and Peyer's patches have also been suggested to take place, but have not yet been

conclusively shown (150). In contrast *C. glabrata* invasion of the epithelial barrier does not involve hyphae formation. It may reach the bloodstream through breaches created *via* trauma, surgery or catheters (19), however, alternative invasion mechanisms have also been suggested. It was shown, for example, that *C. glabrata* can bind to *C. albicans* hyphae in order to establish colonization or infection in an OPC mice model (462) and may therefore hijack the *C. albicans* translocation machinery. In another recent study, it was shown that a single human protein, albumin, can dramatically enhance the pathogenic potential of *C. glabrata* on vaginal epithelial cell by a combination of beneficial effects for the fungus, which includes an increased access to iron, accelerated growth, and increased adhesion (463). Furthermore, it was shown that *C. glabrata* and other non-hyphae forming *Candida* spp. bind to bridging molecules present in human serum to invade the epithelial barrier *via* bridging molecule-mediated endocytosis (464). In general, *C. glabrata*'s invasion tactics are not well studied, and more research is needed to better understand how the fungus can take advantage of other microbes or the host itself to achieve invasion. Further details about the adhesion, invasion, and damage potential of *Candida* species have been extensively discussed in past reviews (370, 465-467).

Interaction with Host Cells

Once invasion occurs, the host's immune response will be activated (see above). Both *C. albicans* and *C. glabrata* can be recognized *via* PRRs and are phagocytosed by macrophages and other myeloid cells. They are both able to delay phagosome maturation to avoid killing, although the main mechanism of *C. albicans* to escape detrimental intracellular effect is the formation of hyphae and a fast escape from the macrophages (26, 468, 469). However, escape from macrophages *via* hyphae formation has only been seen

in vitro and as of yet, there is no validation in a mammalian model. In contrast, *C. glabrata*, similar to certain bacteria such as *Mycobacterium tuberculosis* (470), can persist and replicate in the phagosome until the phagocyte bursts (42, 471). Interestingly, a rare non-lytic escape mechanism called vomocytosis from macrophages has also been reported for *C. albicans*, in which a yeast cell is ejected from the phagocyte without disrupting the phagocyte membrane (472). In a zebrafish infection model, yeast-locked *C. albicans* have been shown to persist in macrophages up to 40 hours and are able to spread in different tissues using the host cells as a Trojan horse (473). Multiple studies have recently shown that *C. albicans* hijacks the inflammasome and pyroptotic pathway to escape from macrophages using candidalysin to facilitate its exit (474, 475). Other types of cell death, such as the induction of apoptosis (476) and necroptosis (477), have been associated with *C. albicans*. Additionally, the induction of anti-apoptotic signals during *C. albicans* infection in macrophages has been described (478). However, it is not yet clear whether regulation of these signals serves the host as a mechanism against the pathogen or the fungus as a virulence factor. In contrast, during *C. glabrata* infection macrophages show little to no cytokine release (42) and the fungus is not able to trigger pyroptosis (290).

C. glabrata depends on its autophagy to persist inside the phagosome (479), probably to compensate for the lack of nutrients inside this organelle. Damage due to oxidative stress in the phagosome is mitigated by the superoxide dismutase, Sod1 (480), and to a lesser extent the catalase, Cta1, which is not essential for survival (481). Interestingly, a recently described transcription factor (Tog1) has been described that links oxidative stress responses with metabolic adaptations to macrophage persistence (482). In an *ex vivo* blood

infection model, *C. glabrata* did not show a significant upregulation of oxidative stress response genes, and while *C. albicans* upregulated the glyoxylate cycle and fermentative energy production, *C. glabrata* even downregulated transporters for different nutrients such as amino acids (483). *Petite* phenotypes of *C. glabrata* show, in addition to their azole resistance, increased endoplasmatic reticulum (ER) stress resistance and survival in phagocytes (110, 112). Similar to *C. glabrata*, *C. albicans* uses superoxide dismutases (Sods) to protect against oxidative stress by detoxification of reactive oxidative species (ROS) (484-486). Mutants of Sod4 and Sod5 showed increased accumulation of ROS and decreased viability inside macrophages and blood cells (484), suggesting killing in a ROS-dependent manner (484, 485).

The *Candida* cell wall consists of an intricate network of polysaccharides and proteins and its composition and structural organization is highly dynamic depending on environment cues and its morphological state (see above). Recognition by immune cells is dependent on PAMP expression, and alterations in the cell wall architecture affect phagocytosis and the release of pro-inflammatory cytokines (487-490). *C. albicans* modulates the exposure of β-1.3 glucan by actively masking this pro-inflammatory PAMP in response to host signals, such as carbon source, lactate and other short chain fatty acids (427, 491), pH (420, 492), hypoxia (493), and iron limitation (494). Avoidance of immune β-1,3 glucan recognition is also achieved by the shaving of cell surface β-1,3 glucan *via* the secreted glucanases, Xog1 (495) and Eng1 (496). Neutrophils counteract masking by NET-mediated attacks, which trigger active remodeling of the fungal cell wall and enhances immune recognition *via* β-1,3 glucan in macrophages (497). However, other immune cells, such as monocytes,

1175 are trained more on mannans in the outer cell wall than β-1,3 glucan (490), and so
1176 expression of the PRR repertoire is immune cell-dependent and tailors immune
1177 recognition.

1178 **Metabolic Interactions**

1179 In general, *C. albicans*' preferred energy source is glucose. However, in specific host
1180 niches or inside phagocytes the fungus can adapt and use alternative energy sources *via*
1181 activating gluconeogenesis and starvation responses. Both *C. albicans* and *C. glabrata* are
1182 able to use two-carbon compounds, such as acetate derived from fatty acids, for
1183 gluconeogenesis (498, 499). This glyoxylate shunt is important for the survival and
1184 virulence of both fungi inside the phagosome. In the glucose-poor environment of the
1185 phagosome, *C. albicans*' proline and arginine catabolism are an important mechanism for
1186 filamentation induction (500). During infection by *C. albicans*, glycolysis,
1187 gluconeogenesis and the glycosylate pathway are required at different times and in
1188 different niches. Normal concentrations of glucose repress the glyoxylate and
1189 gluconeogenesis pathways in the blood but are activated in phagocytes (501, 502). It is,
1190 however, clear that many infected tissues do not behave as a homogenous
1191 microenvironment and that microsites may exist where cells of quite different metabolic
1192 profile exist side by side (501). It is also known that physiological concentrations of
1193 glucose activate an oxidative stress response that promotes fitness downstream, when
1194 *Candida* spp. cells are engulfed by neutrophils (503). This anticipatory behavior enables
1195 the yeast cell to activate and prime its defenses to immune attack before it encounters the
1196 toxic environment of the neutrophil phagolysosome.

C. albicans can acquire iron *via* multiple host sources including hemoglobin, hemin, ferritin, and transferrin (504). When in blood, candidalysin acts as a hemolytic factor for *C. albicans* (505) and allows to utilize hemoglobin *via* the Rbt5/Hmx1 system to acquire iron (506), while *C. albicans* hyphae can also acquire iron *via* the host iron storage molecule, ferritin, through binding to Als3 (507). *C. albicans* regulates its iron uptake tightly depending on environmental iron availability. During iron starvation in the host, for example within the blood during bloodstream infections, the fungus upregulates the expression of *SEF1* (391). Sef1 activates a large set of genes, including *HAP43*, to acquire iron from the environment (508). Hap43, a part of the CCAAT-binding complex, upregulates iron uptake genes and downregulates iron-consuming processes. Additionally, Hap43 represses Sfu1, a GATA family transcription factor (509). This contrasts with the regulation to the iron-rich environments that is described above, where Sfu1 represses iron upregulating genes to avoid iron toxicity (391). *C. glabrata* has a more limited ability to use host iron sources, and lacks a high affinity iron uptake system (510). In iron-poor environments, the Aft1 transcription regulator is activated to upregulate iron uptake and recycling processes (511). At the same time, Cth2 binds to and degrades mRNA involved in iron-consuming processes (511). Interestingly, neither of the two *Candida* species produce their own siderophores and both rely on xenosiderophores e.g., from bacteria or other fungi (510). Nevitt and Thiele identified Sit1, a xenosidephore transporter, which *C. glabrata* uses to survive in the phagosome (512). However, zinc, another essential metal can be sequestered by a sophisticated zincophore system by *C. albicans* (513) .

Zinc and copper are transported into the phagosome by macrophages and both are considered to contribute to ROS production as well as inactivation of many enzymes by mismetallation. *C. glabrata* counteracts this by upregulation of Cu-binding metallothioneins in the presence of high copper levels (514), while *C. albicans* pumps copper out using a P-type ATPase (515). When zinc ions are in excess, *C. glabrata* sequesters zinc to vacuoles *via* the transporter Zrc1 (516). Both species are auxotrophic for biotin and possess a high-affinity biotin transporter, Vht1, which is required for efficient proliferation inside the phagosome *in vitro* and for full virulence of *C. albicans* in a murine systemic infection model (34).

To summarize, both fungi have developed mechanisms to efficiently infect the host and to enable metabolism in a variety of host niches. Both species rely on two-carbon sources and the glyoxylate shunt for survival in the host. They can acquire nutrients such as iron *via* different mechanisms, and can inactivate up-take of non-beneficial nutrients, such as excess copper and zinc, to ensure their survival. The *in vivo* metabolic adaptations show some similarities but also differ in key elements. Further research is needed to better understand these mechanisms especially for *C. glabrata* infections, which are understudied compared to *C. albicans*.

FUTURE STRATEGIES

A major health goal for the future will be to reduce the number of superficial and life-threatening *Candida* spp. infections. To this end, it is necessary to establish better, faster, specific and easily accessible diagnostic tools to detect fungal infections and their drug resistances at an early stage. Techniques such as MALDI-TOF, DNA microarray, and PCR detection have been increasingly used the past years, and these assays are sensitive, but not widely available. They also have potential to provide useful additional clinical information such as an understanding of the resistance genes that a *Candida* spp. strain may harbor.

As yet there are no traditional or next generation RNA vaccines against *C. albicans* or *C. glabrata*, although a fragment of the *C. albicans* GPI-anchored cell wall protein Als3 has shown promise in a phase 2 clinical trial as a monovalent vaccine against recurrent vaginitis (517). β-glucan particles have also been explored as vaccine carriers of fungal antigens (518). It is feasible that polyvalent vaccines will prove to be effective against superficial or systemic disease caused by these two *Candida* species and investment is needed to explore the utility of these unexploited therapeutic strategies.

In medical mycology the use of combinations of antifungal drugs is rare – and most drugs against *C. albicans* and *C. glabrata* are used as monotherapies or in sequential monotherapy. This contrasts with the combinatorial approaches taken in other areas of infectious disease therapy (519) and in agriculture, to broaden the spectrum of coverage and/or suppress the emergence of resistant strains. Future strategies should therefore include exploring how optimized drug combinations might be used that are safe, effective and preserve the durability of antifungals by suppressing antifungal drug resistance. For

example, chitin synthase and β-1,3 glucan synthase inhibitors would be expected to exhibit synergy as a drug combination, and agents that block cell wall salvage pathways, such as the calcineurin pathway, potentiate the action of inhibitors of cell wall biosynthesis at least *in vivo* (520). Membrane acting peptides, applied alone and in combination with azoles, have been shown to be effective in disrupting biofilms (521). Another potential way to successfully control *Candida* spp. infections in the future may be the use of antivirulence drugs. Antivirulence drugs show potential especially against *C. albicans* infections by inhibiting filamentation and biofilm formation (408).

Also, adjuvants or cell wall components that activate or suppress inflammation may be helpful in treating fungal disease. Purified immunomodulatory components of the cell wall have the potential to promote immune recognition and activate B cell and T cell responses that are required for disease suppression. Hyper-inflammatory diseases such as *Candida* spp. vaginitis may be mitigated by blocking the signal cascade that leads to inflammation. Recently a promising advance has been made showing that the *C. albicans* zinc-binding protein Pra1 is a natural attractant for neutrophils and thus promotes inflammatory vaginitis (513, 522). A Pra1 homologue does not exists in *C. glabrata*. Women with recurrent vaginitis often have low zinc levels (523, 524) and exogenous addition of zinc prevented Pra1 production and neutrophil infiltration into the vaginal canal, thus preventing localized inflammatory disease (522). Furthermore, the peptide toxin candidalysin, found in *C. albicans* but not *C. glabrata*, has been shown to be a key hypha-associated virulence determinant responsible for the immunopathogenesis of *C. albicans* vaginitis (459). It was demonstrated that nanobody-mediated neutralization of candidalysin prevents epithelial

damage and inflammatory responses that drive the pathogenesis of vulvovaginal candidiasis (Valentine *et al*., accepted for publication). Future antifungal stewardship strategies may also consider the benefits of combining antifungal drug treatment with immunotherapies.

Empirical, preemptive and prophylactic therapy is widely used for critically ill patients with high susceptibilities to fungal infections and the full use of new generation diagnostics, biomarkers and colonization indices may lead to further improvements in patient care and survival (525). One possible avenue could be the use of probiotics (Live Biotherapeutic Products) to suppress the transition from commensal to the infectious stage (377). This approach may be especially useful in patients with GI tract-related diseases, such as IBD or colitis. Another way to manipulate the microbiome to prevent possible infections or treat overgrowth is through dietary interventions or the use of fecal microbiota transplantation (FMT) that has been used successfully for the treatment of *C. difficile* infections. Promising data has shown that FMT can be effective against *Candida* spp. colonization in the gut (384, 526). Phage therapies have also been suggested as a tool to shape the microbiota and prevent fungal infections. To date phages have not been found that directly target *Candida* spp., their effects on co-habitating bacteria could eliminate fungal pathogens through metabolic interactions either by enhancing bacteria that suppress *Candida* spp. invasion or by eliminating bacteria that enhance *Candida* spp. virulence. As an interesting example for direct fungal-phage interactions, *Pseudomonas* phages can affect *in vitro* growth of *C. albicans*, perhaps by sequestering iron and by direct binding to the fungal surface (527). Such microbiota manipulation techniques have only recently been

developed, and therefore many potential side effects and limitations exist that we may not be aware of. Additional research into these therapies may soon elucidate their true potential against *Candida* spp. infections.

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Bernhard Hube

Bernhard Hube earned his PhD in Microbiology at the University of Goettingen (1991) and spent his postdoctoral time at the University of Aberdeen (1992 – 1995) and the University of Hamburg (1995 – 2000). In 2000 he became Research Group leader and Head of Division “Mycology”, at the Robert Koch Institute, Berlin. In 2006 he was appointed Professor and Chair for Microbial Pathogenicity at the Friedrich Schiller University of

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FIGURE LEGENDS

FIG 1 Epidemiology and types of *Candida* spp. infections. A. *Candida* species causing superficial (purple text) and systemic (red text) infections. Superficial infections affect the skin or mucosal surfaces of the body and are usually not life-threatening. The most common superficial infections include vulvovaginal candidiasis and cutaneous candidiasis. Systemic infections can affect multiple organs including the heart, brain, kidneys and can potentially lead to septic shock. B. Epidemiology of *Candida* species based on SENTRY antimicrobial surveillance program from 2008-2009. *C. albicans* is the most prevalent global species but variability in the prevalence of non-*Candida albicans Candida* (NCAC) species exists between different geographical regions. Additionally, the distribution of *Candida* species can differ in specific patient cohorts between countries.

FIG 2 Morphological plasticity in *C. albicans* and *C. glabrata*. A. Morphological plasticity in *C. albicans*. Yeast and hyphae are probably the most well-investigated growth forms of *C. albicans*, with specific roles in commensalism and infection as described in the main

text. Pseudohyphae are similarly regularly found *in vitro* and *in vivo*, but their role in *C. albicans*-host interaction remains largely unclear. Opaque and shmoo cells are both involved in mating, while both gray and hyphal cells are associated with different types of infections. Chlamydospores are formed on certain carbohydrate rich media and their role in vivo remain unclear. Wor1 and Efg1 are transcriptional regulators of *C. albicans* morphology, controlling the switch between white (yeast), GUT and opaque cells. B. Morphotypes of *C. albicans*. Cell types shown include: budding yeast cells; hyphae (Sudbery, 2011); elongated yeasts forming pseudohyphae (Veses and Gow, 2009); chlamydospores formed from suspensor cells (Staib and Morschhäuser, 2006); enlarged Goliath cells (Malavia *et al*., 2017); mating-competent opaque and gray phenotypes (Liang *et al*., 2020); elongated chemotactic shmoo-mating projections leading to tetraploid zygote (Lockhart *et al*., 2003) and GUT cells suspected to form in the intestine (Pande *et al*., 2013). Scale bars represent 5 µm. Colony morphologies of *C. albicans* namely, a) o-smooth, b) Star, c) Ring, d) Irregular wrinkly, e) Stipple, f) Hat, g) Fuzzy, h) R-smooth (Slutsky et al., 1985). **C.** Morphotypes of *C. glabrata*. Cell types include budding yeasts and elongated pseudohyphae-like structures. Different colony phenotypes in presence of $CuSO_4$ include white and very dark brown. Intermediate variations of brown colonies and wrinkled also exist but are not shown in above image (Lachke *et al*., 2002).

FIG 3 Overview of selected pattern recognition receptors (PRRs) and their signalling pathways involved in immune recognition of *Candida* spp. C-type lectin receptors (Mannose Receptor, DC-SIGN, Dectin-1, Dectin-2, Dectin-3 and Mincle), Toll-like receptors (TLR1, TLR2, TLR3, TLR4, TLR6, TLR7 and TLR9) and NOD-like receptors

(NOD-2 and NLRP3) recognize conserved molecular patterns, termed pathogen-associated molecular patterns (PAMPs) of *Candida* spp. (including; mannan(s), β-1,3-glucan, chitin, candidalysin, secreted aspartic proteases, RNA and DNA). Recognition induces downstream signaling, via different pathways and transcription factors, such as NF-κB, AP1, IRFs and NFAT, and activation of the immune response. MR, mannose receptor; DC-SIGN, Dendritic-cell-specific ICAM3-grabbing non-integrin; Mincle, Macrophage inducible $Ca2^{+}$-dependent lectin receptor; TLR, Toll-like receptor; FcRγ, Fc receptor γ chain; NOD-2, nucleotide binding oligomerization domain containing 2; NLRP3, NLR family pyrin domain containing 3; PLM, phopholipomannan, Saps, secreted aspartic proteases; SYK, spleen tyrosine kinase; PKCδ, protein kinase Cδ; PLCγ, phospholipase C γ; CARD9, caspase activation and recruitment domain-containing 9; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein 1; Bcl10, B-cell lymphoma/leukemia 10; MyD88, myeloid differentiation primary response 88; IRAK, interleukin-1 receptor (IL-1R) associated kinase; TRAF, TNF receptor associated factor; TRIF, TIR-domain-containing adapter-inducing interferon-β; MAPK, mitogen-activated protein kinase; IL, interleukin; NFAT, Nuclear factor of activated T-cells; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; AP1, activating protein-1; IRF, Interferon regulatory factor.

FIG 4 From commensal to pathogen. *C. albicans* and *C. glabrata* can reside in the human body as commensals in balance with the microbiome. *C. albicans* can be found as both yeast and hyphae on the gut mucosal surfaces and hyphal-associated genes e.g., *UME6* have been shown to play an important role during commensalism. The iron-rich

environment of the gut leads to downregulation of iron acquisition processes to avoid toxicity. During commensalism, the host cells activate the NF-κB pathway independent of the fungal morphology. Immunosuppression, the use of antibiotics or physical damage of the epithelial barrier are among the predisposing factors for *Candida* spp. infections. *C. albicans* adheres to epithelial cells using adhesins such as Als3, followed by invasion *via* induced endocytosis (triggered by Als3) or active penetration (by physical forces), leading to either transcellular or paracellular invasion. The transcellular route can cause severe candidalysin-mediated cellular damage, however, moderate damage can be repaired by epithelial cells. In addition to candidalysin, the fungus can secrete an arsenal of hydrolases (e.g., proteases and lipases). *C. glabrata* invades the epithelial barrier either *via* damaged barriers or by exploiting invading *C. albicans* hyphae in co-infections. Epithelial cells invaded by hyphal cells and damaged by candidalysin activate the MKP1/c-FOS pathway, which leads to the production of cytokines and attraction of phagocytes. Once inside the lamina propria both fungi can get phagocytosed by resident macrophages *via* recognition of PAMPs (β-1,3- glucan, mannan). Inside the phagosome, fungal cells use superoxide dismutases to detoxify reactive oxygen species. Phagocytosis of *C. albicans* cells by macrophages triggers the production of high levels of several cytokines, while phagocytosis of *C. glabrata* causes the secretion of only low levels of GM-CSF. Internalised *C. albicans* cells produce hyphae, induce pyroptosis, secrete candidalysin, which leads to the activation of the NLRP3 inflammasome, and escape from the phagocyte. Cytokine production from both epithelial cells and macrophages, recruits further phagocytes (neutrophils, macrophages, dendritic cells) from the bloodstream. Phagocytosis by dendritic cells activates Th17 immunity and the production of IL-17 and IL-22. IL-17

promotes neutrophil trafficking and IL-22 contributes to integrity of the epithelial barrier and production of antimicrobial peptides. *C. albicans* can further adhere to the endothelium and invade and translocate from there to cause bloodstream infections (BSI).

FIGURES

FIGURE 1

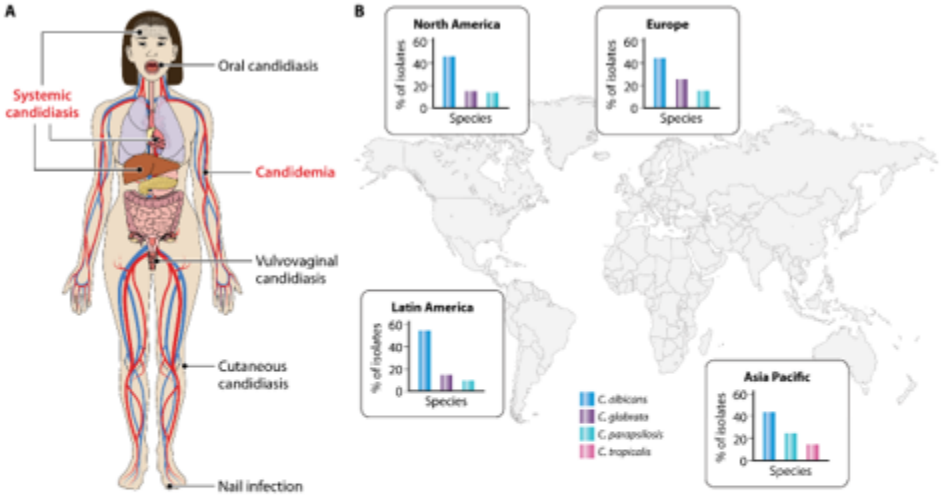

FIG 1. Epidemiology & types of *Candida* spp. infections. A. *Candida* species causing superficial (black text) and systemic (red text) infections. Superficial infections affect the skin or mucosal surfaces of the body and are usually not life-threatening. The most common superficial infections include vulvovaginal candidiasis and cutaneous candidiasis. Systemic infections can affect multiple organs including the heart, brain, kidneys and can potentially lead to septic shock. B. Epidemiology of *Candida* species based on SENTRY antimicrobial surveillance program from 2008-2009. *C. albicans* is the most prevalent global species but variability in the prevalence of non-*Candida albicans Candida* (NCAC) species exists between different geographical regions. Additionally, the distribution of *Candida* species can differ in specific patient cohorts between countries.

FIGURE 2

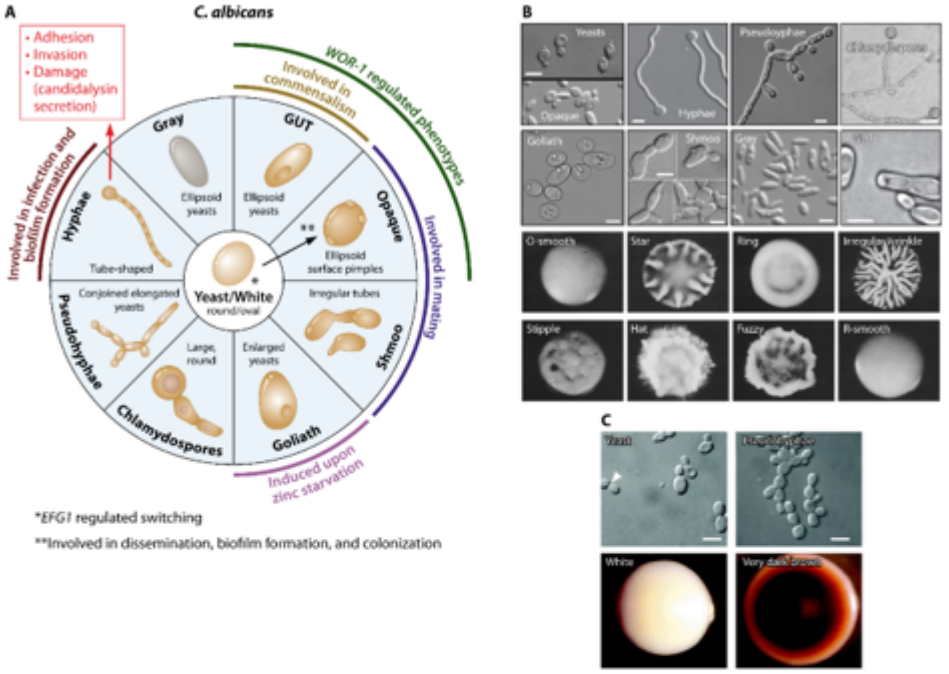

FIG 2. Morphological plasticity in *C. albicans* and *C. glabrata*. A. Morphological plasticity in *C. albicans*. Yeast and hyphae are probably the most well-investigated growth forms of *C. albicans*, with specific roles in commensalism and infection as described in the main text. Pseudohyphae are regularly found *in vitro* and *in vivo*, but their role in *C. albicans*-host interaction remains largely unclear. Opaque and shmoo cells are both involved in mating, while both grey and hyphal cells are associated with different types of infections. Chlamydospores are formed on certain carbohydrate rich media and their role *in vivo* remains unclear. Wor1 and Efg1 are translational regulators of *C. albicans* morphology, controlling the switch between white (yeast), GUT and opaque cells. B. Morphotypes of *C. albicans*. Cell types shown include: budding yeast cells; hyphae (Sudbery, 2011); elongated yeasts forming pseudohyphae (Veses and Gow, 2009); chlamydospores formed from suspensor cells (Staib and Morschhäuser, 2006); enlarged Goliath cells (Malavia *et al*., 2017); mating-competent opaque and grey phenotypes (Liang *et al*., 2020); elongated chemotactic shmoo-mating projections leading to tetraploid zygote (Lockhart *et al*., 2003) and GUT cells suspected to form in the intestine (Pande *et al*., 2013). Scale bars represent 5 µm. Colony morphologies of *C. albicans* namely, a) o-smooth, b) Star, c) Ring, d) Irregular wrinkly, e) Stipple, f) Hat, g) Fuzzy, h) R-smooth (Slutsky et al., 1985). C. Morphotypes of *C. glabrata*. Cell types include budding yeasts and elongated pseudohyphae-like structures. Different colony phenotypes in presence of $CuSO_4$ include white and very dark brown. Intermediate variations of brown colonies and wrinkled also exist but are not shown in above image (Lackhe *et al*., 2002).

FIGURE 3

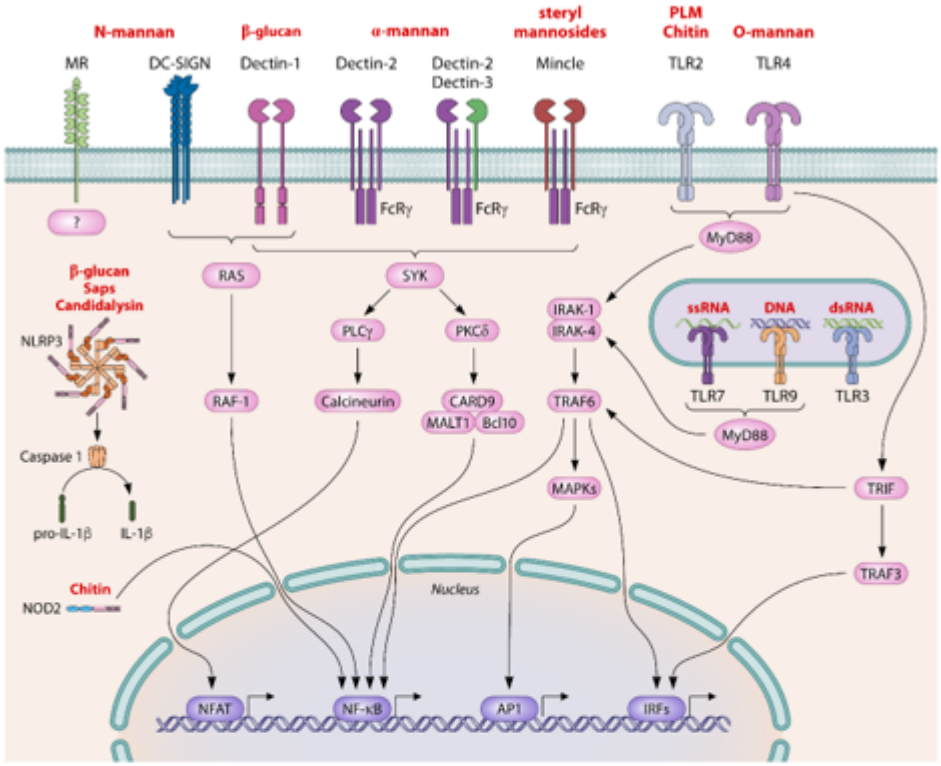

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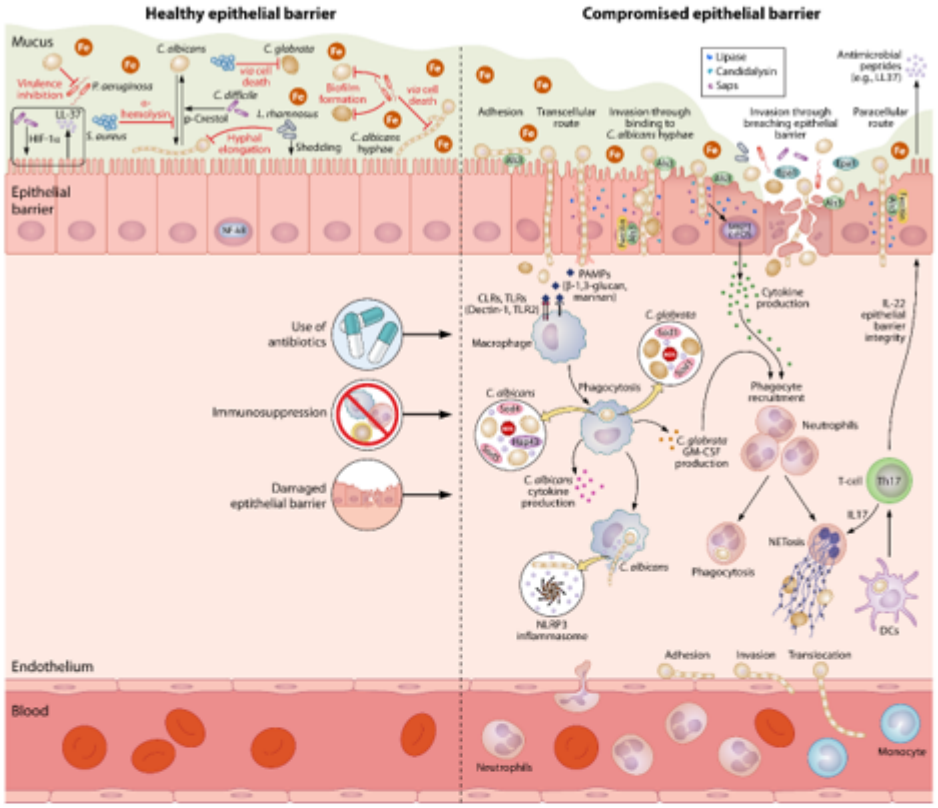
FIGURE 4



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