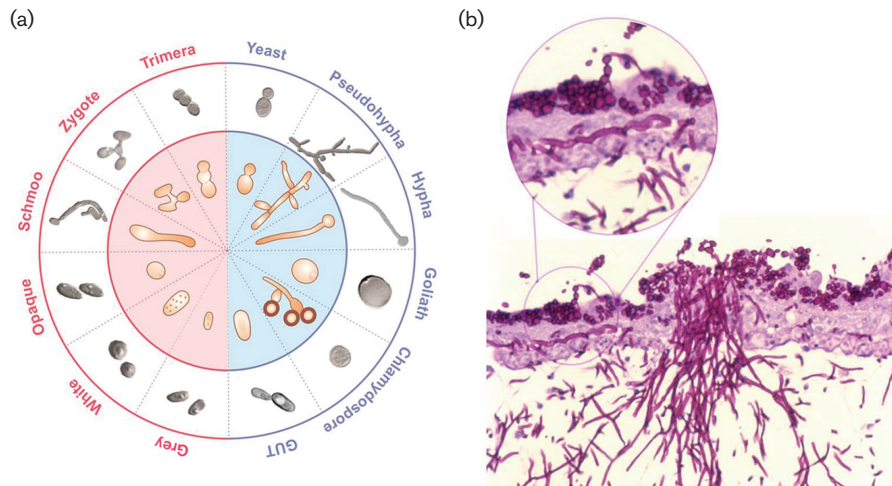


Microbe Profile: *Candida albicans*: a shape-changing, opportunistic pathogenic fungus of humans

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Graphical abstract

(a) Morphotypes of *Candida albicans* (blue sector, vegetative forms; pink sector, forms related to mating or changes in ploidy). Cell types shown include: budding yeast cells; elongated conjoined yeasts forming pseudohyphae; parallel-sided hyphae; chlamydospores formed from suspensor cells; enlarged goliath cells formed under zinc deprivation (unpublished study, image from Duncan Wilson); intestinal gut form cells (image from Suzanne Noble); mating competence defined by white–grey–opaque cell transitions (images from Guanghua Huang); elongated chemotactic shmoo-mating projections leading to tetraploid zygote formation (images from David Soll and Karla Daniels); trimera formed by unequal chromosome segregation under antifungal exposure (image from Judith Berman). (b) Superficial yeast colonization and invasion of the chicken chorioallantoic membrane by *C. albicans* hyphal cells.

Abstract

Candida albicans is normally a harmless commensal of human beings, but it can cause superficial infections of the mucosa (oral/vaginal thrush) in healthy individuals and (rarely) infections of the skin or nails. It can also become invasive, causing life-threatening systemic and bloodstream infections in immunocompromised hosts, where the mortality rate can be as high as 50%. It is the most common cause of serious fungal infection and is a common cause of nosocomial infections in hospitals. Some strains have been recognized that are resistant to azoles or echinocandins, which are the first-line antifungals for treatment of *C. albicans* infections.

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Keywords: *Candida albicans*; pathogenesis; Medical Mycology; morphogenesis; immune response; drug resistance.

Abbreviations: MYA, million years ago; RNS, reactive nitrogen species; ROS, reactive oxygen species; Th, T helper cells.

TAXONOMY

First description in 1839 by Langenbeck. *Candida* – Latin *candidus*, meaning ‘gleaming white’; *albicans* – Latin *albi-care*, meaning ‘to whiten’, suggestive of the white exudate on the infected mucosal surfaces.

Superkingdom Eukaryote, kingdom Fungi, subkingdom Dikarya, phylum *Ascomycota*, subphylum *Saccharomycotina*, class *Saccharomycetes*, subclass *Saccharomycetidae*, order *Saccharomycetales*, family *Metschnikowiaceae*, genus *Candida*, species *albicans*.

PROPERTIES

C. albicans is highly polymorphic (see the graphical abstract), switching *in vivo* to alternative vegetative growth forms in response to changing environmental conditions such as nutrient availability, temperature, pH, CO₂ and the presence of serum [1]. This phenotypic flexibility is an important virulence factor that aids in its invasion of epithelia, dissemination throughout the host and survival in different host niches, and also helps to modulate the host immune response and counteract immune surveillance. It is highly metabolically flexible and can utilize different nutrient sources simultaneously through post-transcriptional rewiring and constitutive expression of alternative metabolic pathways [2].

GENOME AND EVOLUTION

C. albicans was one of the first eukaryotic pathogens to have its genome sequenced [3]. Clinical isolates have a 16 Mb genome, with 33.3% GC content, 132 non-coding RNAs, a number of transposons, 8 diploid chromosomes and 6735 (haploid) ORFs. The *C. albicans* genome is highly plastic and high levels of heterozygosity, intra-chromosome recombination and aneuploidy can be observed between genomes of different strains. The loss of heterozygosity, chromosomal rearrangements and whole chromosome or segmental aneuploidies lead to stress adaptation and can also affect drug sensitivity by influencing the copy number of key drug-resistance alleles [4]. Many key virulence-associated functions are performed by multi-gene families, some of which have evolved by sub-telomeric gene duplication and expansion.

Even though haploid forms of *C. albicans* have been identified [5], and fusion of opposite mating types has been observed [6], no full meiotic sexual cycle has been discovered. The populations observed in a single host are mostly clonal in nature. Under stressful environmental conditions it has been shown to undergo a parasexual cycle where two diploids of opposite mating types fuse to form tetraploid zygotes that undergo concerted chromosome loss to give rise to near diploids.

PHYLOGENY

C. albicans belongs to a limited CTG clade of asexual *Candida* species in the *Saccharomycetales* order, which decode

the codon CTG as Ser instead of Leu [7], resulting in practical difficulties in expressing heterologous gene sequences. Whole-genome sequence analysis and comparisons with other *Candida* species of the CTG clade have shown the expansion of many gene families, conferring pathogenicity, by gene duplication in *C. albicans* which makes it the most pathogenic of the *Candida* species. The closest relative is *Candida dubliniensis*, although there is no correlation between phylogeny and relative virulence. Some other pathogenic *Candida* species are haploid.

KEY FEATURES AND DISCOVERIES

C. albicans lives asymptotically as a commensal of warm-blooded animals. No environmental reservoirs are known. It is transmitted from mothers to neonates and by nosocomial infection. Between 30–70% healthy individuals carry at least one *Candida* species commensally. However, it causes life-threatening and fatal bloodstream and invasive systemic infections in immunocompromised individuals and upon breaching of protective mucosal barriers during trauma and surgical interventions. This is also promoted when the suppressive host microbiota is inhibited [8].

During the course of infection, *C. albicans* can manipulate the host immune response by altering its cell-wall components, changing cell shape and secreting various virulence factors. Its cell wall is a bilaminar structure composed of outer fibrillar mannoproteins and an inner core of β -glucans and chitin that all contribute to the immune response. Changes in the structure and composition of the wall occur in different host microenvironments and in response to the action of antifungal drugs. This can prevent or interfere with phagocytosis and inhibit or modulate the protective Th1, Th17 and inflammasome immune responses, and activate the anti-inflammatory Th2 response, leading to tolerance [9]. Phagocytosed yeasts can form hyphae and induce pyroptosis (a form of apoptosis caused by NLRP3 inflammasome activation). Even if phagocytosed, it has the ability to induce its own non-lytic expulsion and prevent acidification and maturation of the phagolysosomes of macrophages, and to express detoxifying enzymes to counteract ROS/RNS-induced damage in the phagosome.

It expresses invasins that induce its uptake by epithelial cells, and adhesins that confer the ability to adhere to several biotic and abiotic surfaces (such as medical implants and catheters), and forms drug-resistant biofilms. It also secretes several hydrolytic enzymes (e.g. proteases and lipases), zinc-scavenging proteins and a pore-forming toxin called candidalysin [10], which aids tissue penetration and results in damage of host epithelia and activation of immune responses.

C. albicans can inhibit host complement activation, inactivate antimicrobial peptides and inhibit other immune cell functions, thus weakening host defences. Antifungal drugs targeting cell-wall β -1,3 glucan (echinocandins) or the ergosterol biosynthesis pathway (azoles) are used as first-line options to treat infection, but *C. albicans* can develop

resistance via the upregulation of azole efflux pumps, the acquisition of mutations affecting the structure or expression of the azole target CYP51 (cytochrome P450 lanosterol 14 α -demethylase), or the induction of compensatory changes in chitin in the cell wall in response to echinocandins.

OPEN QUESTIONS

- An in-depth understanding of the determinants of pathogenicity, adaptability and fitness of *C. albicans* needs to be developed.
- The roles of many of the cell-wall proteins and other surface components in the immune response and in disease are not fully understood.
- Studies of the variability in individual host responses and the influence of human genetic polymorphisms in determining the outcome of *Candida* infections is generating opportunities to design personalized therapeutic options.
- Diagnostics that distinguish commensal carriage and invasive disease are needed. High mortality is often associated with failure to make an early and accurate diagnosis.
- Research towards developing an anti-*Candida* vaccine is urgently required.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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