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Review

Overview of selected virulence attributes in *Aspergillus fumigatus*, *Candida albicans*, *Cryptococcus neoformans*, *Trichophyton rubrum*, and *Exophiala dermatitidis*

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ABSTRACT

The incidence of fungal diseases has been increasing since 1980, and is associated with excessive morbidity and mortality, particularly among immunosuppressed patients. Of the known 625 pathogenic fungal species, infections caused by the genera *Aspergillus*, *Candida*, *Cryptococcus*, and *Trichophyton* are responsible for more than 300 million estimated episodes of acute or chronic infections worldwide. In addition, a rather neglected group of opportunistic fungi known as black yeasts and their filamentous relatives cause a wide variety of recalcitrant infections in both immunocompetent and immunosuppressed hosts. This article provides an overview of selected virulence factors that are known to suppress host immunity and enhance the infectivity of these fungi.

1. Introduction

Since 1980, the incidence of invasive fungal diseases has increased significantly in both humans (Baddley et al., 2001; Guinea, 2014; Marr, 2010; Pagano et al., 2006; Petrikkos et al., 2014; Rajasingham et al., 2017) and animals (Seyedmousavi et al., 2013, 2014, 2015). Many well-known risk factors of human invasive mycoses have been described, such as human immunodeficiency virus infection (Armstrong-James et al., 2014; Rajasingham et al., 2017), organ transplantation (Neofytos et al., 2010; Pappas et al., 2010), and treatment in intensive care units (Tortorano et al., 2012). The importance of fungal infections is becoming increasingly recognized with a rise in the number of immunosuppressed patients that are most at risk and with development of new diagnostic techniques. Among these pathogenic species, *Aspergillus fumigatus*, *Candida albicans*, and *Cryptococcus neoformans* are relatively well studied. However, medical mycologists have also shown an increasing interest in rather neglected groups of fungi such as *Exophiala dermatitidis* and *Trichophyton rubrum*, which can infect both immunocompetent and immunosuppressed individuals (Kuklová et al., 2011; Li and de Hoog, 2009). *E. dermatitidis* (order Chaetothyriales) is commonly associated with fatal cerebritis, an infection of the brain that often leads to abscess formation, in immunocompetent individuals, particularly in South-east Asia (Li and de Hoog, 2009), whereas *T. rubrum* causes mainly chronic and recurrent superficial infections that may affect the patient's psychology and social life (Gupta and Nakrieko, 2015; Kong et al., 2015). Thus, it is crucial to study the interaction between a host and fungus for exploring their virulence potential and relative capacities to cause disease in a susceptible host (Casadevall and Pirofski, 1999, 2001).

Here, we provide an overview of our current understanding of the selected virulence factors responsible for the infections of five major human fungal pathogens: *A. fumigatus*, *C. albicans*, *C. neoformans*, *T. rubrum*, and *E. dermatitidis* (Table 1).

2. Aspergillus fumigatus

The genus *Aspergillus* has been subdivided into four subgenera (*Aspergillus*, *Circumdati*, *Fumigati*, and *Nidulantes*) and 20 sections including 339 recognized species at present (Houbraken et al., 2014; Hubka et al., 2015; Samson et al., 2014). Nevertheless, only a few well-

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Table 1
Taxonomy, clinical presentations, virulence factors, mating type, and epidemiological characteristics of the main pathogenic fungi.

Phylogenetic classification		Fungal pathogens	Infections	Grovvth at 37 °C	Growth at 42 °C	Growth at 48 °C	Melanin	Capsule	Biofilm formation	Dissemination to brain	Colony morphologies/ morphogenesis	Enzymes	Secondary metabolites known as virulence factors	Mating type	Annually reported case numbers
Phylum Ascomycota	Subphylum Pezizomycotina	*Aspergillus fumigatus*	Invasive, chronic, and allergic infections	+	+	+	+	−	+	+	+	Proteases, Phospholipases. Lipases, Superoxide dismutase, Catalase	Gliotoxin	Contradictory results but studies with congenic strains suggest that mating type is not related to virulence	Over 250,000 cases of IA annually and global estimates suggest that over 3 million patients have CPA, and 4,8 million suffer from ABPA
	Saccharomycotina	*Candida albicans*	Mucocutaneous to disseminated chronic and invasive infections	+	+	−	−	−	+	−	Yeast to hyphae transition, Opaque-white cell switching, Colony switching	Superoxide dismutase, Catalase	Candidalysin, Siderophores	MTL heterozygous strains more virulent than MTL homozygous or haploid strains	> 400,000
	Pezizomycotina	*Trichophyton rubrum*	Skin and nails infections	+	−	−	Possible roles in pathogenesis are not known	−	+	Extremely rare dissemination to deeper tissues, but it can spread to other superficial anatomical sites	−	Multiple secreted serine and metallo-endoproteases, Phospholipases, Lipases, Laccase	Haemolysin, Xanthomegnin. Aflatoxin-like substances, Lipophilic	Possible roles in pathogenesis are not known	In the developed world, 10% of the population may be expected to have tinea pedis and/ or tinea unguium, approximately 70% would be *T. rubrum* infections
	Pezizomycotina	*Exophiala dermatitidis*	Pulmonary colonization in CF patients and invasive (fatal cerebritis) infections	+	+	−	Pigmentation, Antioxidant, prevent desiccation and UV radiation damage	Enhances adhesion to smooth surfaces	±	+	True- or pseudo-hyphae, Mold-like and yeast-like forms, Sclerotic bodies	Catalase, Urease	Siderophores	Possible roles in pathogenesis are not known	−

(*continued on next page*)

Table 1 (*continued*)

Phylogenetic classification		Fungal pathogens	Infections	Growth at 37 °C	Growth at 42 °C	Growth at 48 °C	Melanin	Capsule	Biofilm formation	Dissemination to brain	Colony morphologies/ morphogenesis	Enzymes	Secondary metabolites known as virulence factors	Mating type	Annually reported case numbers
Basidiomycota	Basidiomycotina	*Cryptococcus neoformans*	CNS and Pulmonary infections	Dependent upon calcineurin	–	–	Fungal survival in CSF, Protection from oxidative damage, Resistance to certain antifungal drugs	Biofilm formation, Inhibition of leukocyte migration, Suppression of T lymphocyte Proliferation, Induces IL-10 secretion, Reduces systemic inflammation, Inactivation of complement and antibody response	+	From lung to brain by (i) Paracellularly; (ii) Transcellularly; or (iii) "Trojan horse" mechanism	Titan cells (can be 100 pm), Colony switching	Laccase, Urease, Serine protease, Phospholipase B, Ferroxidase	–	α mating type can be more virulent than **a** in certain genetic backgrounds	223,100 cases of Cryptococcal meningitis

IA, invasive aspergillosis; CPA, chronic pulmonary aspergillosis; ABPA, allergic bronchopulmonary aspergillosis; *MTL*, mating type locus; CF, cystic fibrosis; CNS, Central nervous system; CSF, cerebrospinal fluid.

known species (e.g., *A. fumigatus* and *A. flavus*) are considered important opportunistic pathogens in humans and animals (Kwon-Chung and Sugui, 2013). In humans, *A. fumigatus* is the most common and life-threatening airborne opportunistic fungal pathogen, with particular significance among immunosuppressed hosts (Kwon-Chung and Sugui, 2013).

2.1. Mycotoxins

Mycotoxins are the virulence factors of *Aspergillus* that suppress host immunity, thereby enhancing the infectivity of the fungus (Bok et al., 2006; Coméra et al., 2007). *Aspergillus* produces several well-known mycotoxins, including aflatoxins, gliotoxin, and ochratoxin A (Bossou et al., 2017; Samson et al., 2014). Aflatoxins and ochratoxins are the most toxic products and have been shown to be genotoxic, i.e., can damage DNA and cause cancer in humans. According to their structure, aflatoxins are difuranocoumarol lactons, with approximately 20 derivatives identified to date. Aflatoxin (AF) B1, B2, G1, and G2 are the most frequent form, with decreasing toxicity in the order AFB1 > AFG1 > AFB2 > AFG2. Ochratoxins are polyketid derivatives of dihydroisocoumarin, including ochratoxin A (OTA, the most toxic), B, C (an ethylester OTA), and D (Bennett and Klich, 2003; Kensler et al., 2011).

Gliotoxin, a secondary metabolite of *A. fumigatus*, has attracted the most interest because of its potent immunosuppressive and cytocidal properties. Moreover, it is mostly produced in the early stage of infection, and is readily detected during experimental infections and in sera from patients with aspergillosis (Kwon-Chung and Sugui, 2013; Lewis et al., 2005). The contribution of gliotoxin to the virulence of *A. fumigatus in vivo* was first characterized using mutants of two genes involved in gliotoxin biosynthesis: the transcriptional regulator gliZ and the non-ribosomal peptide synthetase gliP (Spikes et al., 2008). One study also showed that gliotoxin was not required for virulence in an immunosuppressed host with an invasive pulmonary infection (Cramer et al., 2006). However, gliotoxin did potentiate the virulence when some neutrophil function was present, raising the possibility that neutrophils are the major target of this toxin (Sugui et al., 2007).

2.2. Thermotolerance

A. fumigatus has been isolated from a wide range of environments, with an optimal temperature of 37 °C (ranging from 12 °C to 65 °C), and the pH of growth sites ranging between 2.1 and 8.8 (Kwon-Chung and Sugui, 2013). The thermotolerance of this species facilitates its growth, not only in decaying organic matter (its primary ecological niche) but also within the mammalian or avian respiratory tract (Seyedmousavi et al., 2015).

There is some evidence that certain nucleolar proteins might mediate the link between thermotolerance and virulence. For example, *cgrA* mutants show a decreased growth rate above 28 °C and are unable to germinate above 48 °C (Bhabhra et al., 2004). In addition, *hrdA* deletion, resulting in a defective endoplasmic reticulum-associated degradation pathway, has an adverse effect on the thermotolerance of *A. fumigatus* (Krishnan et al., 2013).

2.3. Production of extracellular enzymes

The presence of numerous genes encoding glycosyl hydrolases that have the ability to degrade polysaccharides from plant cell walls (Tekaia and Latgé, 2005), as well as a group of extracellular proteinases (i.e., lipases, the endopeptidase PEP2, and the metallopeptidase MepB) in the *A. fumigatus* genome that allow for the assimilation of proteinaceous substrates to acquire nitrogen sources (Croft et al., 2016), attests to the ability of the fungus to grow in a wide variety of environments and substrates (Farnell et al., 2012). Besides these extracellular enzymes, the importance of one of the cellular enzymes,

farnesyltransferase, in *A. fumigatus* was recently reported. The β-subunit of the enzyme RamA is known to affect hyphal branching, germination, and conidial viability. Moreover, in neutropenic murine models of invasive aspergillosis, RamA-deficient strains showed attenuated virulence relative to that of wild-type strains (Norton et al., 2017). Similar to most medically relevant fungi, several enzymes in *A. fumigatus* play a role during fungal growth and development to overcome harsh conditions in the host. Although some of these enzymes such as hexokinase (HxkA), glucokinase (GlkA), and alcohol dehydrogenase (Adh) have been investigated and found to be related to virulence, there is a need for further *in vivo* experiments to assess their specific roles (Fleck and Brock, 2010; Grahl et al., 2011).

2.4. Conidia characteristics and adherence

A. fumigatus conidia are globose to subglobose with a size that is small enough to bypass mucociliary clearance and reach the lower airways (2–3 μm in diameter, with extremes up to 3.5 μm) (Kwon-Chung and Sugui, 2013). The cell wall of these conidia is composed of a hydrophobic protein layer containing the hydrophobin RodA, which masks fungal molecular recognition patterns (Carrion et al., 2013). Inhaled conidia of *A. fumigatus* rapidly adhere to pulmonary epithelial cells and other host constituents (Escobar et al., 2016). This adhesin function in *Aspergillus* is mediated by the fungal carbohydrate components of the cell wall and extracellular matrix (ECM), which are distinct from the adhesin proteins of *C. albicans*. The conidia themselves also contain other known adhesins such as galactosaminogalactan (GAG) (Gravelat et al., 2013), fucose-specific lectin A (FleA), the extracellular thaumatin domain protein AfCalAp (important for the early stage of germination and interaction with host cells), and sialic acid-specific lectin (to bind laminin and fibronectin) (Croft et al., 2016). In addition, *A. fumigatus* conidia have more sialic acid (for binding ECM proteins) than other aspergilli (Kwon-Chung and Sugui, 2013).

2.5. Melanin

The presence of melanin in the conidial cell wall protects the *A. fumigatus* conidia from phagocytosis (Hillmann et al., 2015), ultraviolet light, and reactive oxygen species (ROS) (Heinekamp et al., 2013). In addition, alveolar epithelial cells internalize a greater number of melanized than non-melanized conidia (Amin et al., 2014), whereas the non-melanized conidia are more readily phagocytosed by phagocytic cells (Thywißen et al., 2011; Volling et al., 2011). Melanin also activates platelets to releases granules (Rambach et al., 2015). However, the metabolic pathways to produce melanin differ widely among *Aspergillus* species. For example, *A. fumigatus* conidia synthesize DHN melanin from 1,8 dihydroxynaphtalene, which influences acidification in phagolysosomes, whereas *A. niger* conidia do not (Escobar et al., 2016). This difference might explain why *A. fumigatus* is a more successful human pathogen than other *Aspergillus* species.

2.6. Cell wall structure

GAG is a principal mediator of *A. fumigatus* virulence and plays a key role in facilitating adherence of the fungus to host constituents. Both early- and late-stage hyphal growth and lack of GAG result in an increase in the inflammatory response and decrease in epithelial cell damage (Gravelat et al., 2013). These findings underscore the importance of GAG in the pathogenesis of aspergillosis, suggesting the potential value of anti-GAG therapeutic strategies (Gravelat et al., 2013).

2.7. Hypoxia and iron utilization

During infection, *Aspergillus* species must be able to tolerate and overcome diverse *in vivo* microenvironmental stress conditions (Emerson et al., 2012), some of which are strongly interconnected. For example, oxygen and iron availability are intimately linked to fungal virulence and the response to existing therapeutics. *Aspergillus* species may develop a coordinated regulatory system in response to hypoxia and iron starvation through modulating the expression of hypoxia- and iron-responsive genes via cross-linked key regulators and/or the regulation of factors involved in ergosterol biosynthesis (Seyedmousavi et al., 2015).

2.8. Signaling pathways

Sensing of changes in the natural habitats or host environment induces significant signaling pathways [i.e., mitogen-activated protein kinase (MAPK) cascades (MPKA, MPKB, and SAKA/MPKC), calcineurin, cyclic adenosine monophosphate (cAMP), and target of rapamycin (TOR) pathways] in fungi, which allow them to adapt quickly to new conditions (Latgé et al., 2017). The MAPK cascades include several pathways such as the high-osmolarity glycerol (HOG) and the cell wall integrity (CWI) pathways (Dirr et al., 2010; Nikolaou et al., 2009), which play significant roles in fungal growth, mating type differentiation, and the stress response to antifungals (Altwasser et al., 2015; Valiante et al., 2015).

Calcineurin shows good potential as a drug target, and therefore its role in fungal pathogenesis has been extensively investigated. Calcineurin plays several crucial roles in filamentous fungi, including in cell wall integrity, adaptation to stress, and hyphal regulation (Juvvadi et al., 2014). In *A. fumigatus*, deletion of *cnaA*, which encodes a catalytic subunit of calcineurin, results in an unusual hyphal morphology (blunted, hyper-branched, with irregularly spaced septated hyphae) (Juvvadi and Steinbach, 2015). The calcineurin catalytic subunit interacts with heat shock protein 90 (Hsp90), which plays an important role in temperature-dependent cell signaling (Brown and Goldman, 2016) and is also essential for hyphal development and proliferation (Lamoth et al., 2012). Deletions in the cAMP pathway lead to a reduction of conidiation and growth rate of *A. fumigatus* (Fuller et al., 2011). The TOR pathway was recently shown to be related with an iron deficiency stress response by regulating ornithine/arginine biosynthesis in *A. fumigatus* (Baldin et al., 2015).

2.9. Biofilm formation

One of the most remarkable features of chronic and invasive *A. fumigatus* infections is biofilm formation, and there are several reports of *A. fumigatus* infections related to the use of bio-materials (Ballazhi et al., 2015; Escande et al., 2011; Jeloka et al., 2011; Mehta et al., 2010). Biofilm formation is important for resistance to the host immune response and antifungal drugs. This structure relies on GAG, ECM, and α-1,3-glucans, and mainly occurs in hyphal forms (González-Ramírez et al., 2016). The ECM is a crucial component of biofilms, and contains melanin, proteins, polysaccharides, and extracellular DNA. Together with this matrix, efflux pumps underpin the cellular resistance of biofilms to antifungal drugs, which can be up to 1000-fold higher than the observed resistance in planktonic forms. The efflux pumps also function to maintain homeostasis and remove toxic substrates in *A. fumigatus* biofilms (Tseung and Zhao, 2016).

2.10. Mating type

A. fumigatus was originally considered an asexual fungus until its sexual state was discovered after six months of incubation on oatmeal agar in the dark (O'Gorman et al., 2009). Two compatible isolates are needed for sexual reproduction, one with a *MAT1-1* allele and the other with a *MAT1-2* allele. Several studies have addressed a possible role of the *MAT* locus in the pathogenicity of *A. fumigatus*. Although Paoletti et al. (2005) found an approximate 1:1 distribution of *MAT1-1* to *MAT1-2* strains among clinical and environmental isolates, Alvaréz-

Perez et al. (2010) determined that the *MAT1-1* mating type was associated with isolates of invasive and clinical origin, as well as with pathogenicity in terms of elastase activity. In another study, Cheema and Christians (2011) found a correlation between the *MAT1-1* mating type and virulence in a *Galleria mellonella* model of infection.

In the most recent study examining whether the mating type is associated with virulence, two isogenic strains of *A. fumigatus* were obtained by successive backcrosses that should differ only in their mating type (Losada et al., 2015). These isogenic strains were used to infect different animal models, but no significant difference in virulence was observed. Further studies with isogenic strains in different genetic backgrounds would allow for more detailed exploration of a potential role of *MAT* in the virulence of *A. fumigatus*.

3. Candida albicans

The genus *Candida* consists of nearly 377 species under the *Saccharomycetales incertae sedis* family. However, only relatively few members of this genus are opportunistic and nosocomial fungal pathogens worldwide, including *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. dubliniensis* (McManus and Coleman, 2014).

Intact barrier function is an essential feature of host defense against candidiasis; when barriers to the outside world are damaged or breached by the insertion of medical devices or surgery, a portal of entry is provided for pathogens such as *C. albicans* (Jabra-Rizk et al., 2016). The virulence of *Candida* species is correlated with the ability to adhere to epithelial cells (especially *C. albicans*) or plastic polymers such as those used for intravascular or urethral catheters (*C. tropicalis*). The fungus is capable of secreting proteinases and lipases that can promote invasion, although the clinical importance of these enzymes is not yet clear (Ells et al., 2014; Trofa et al., 2011).

3.1. Adhesion

Adhesion is the most critical stage of colonization and is the first step of the potential disease course (Hoyer and Cota, 2016). The main *C. albicans* adhesins are encoded by agglutinin-like sequences (Als proteins) (Hoyer and Cota, 2016; Murciano et al., 2012). Other proteins also play a role in adhesion, including hyphae wall protein 1 (Hwp1); plasma membrane receptor integrin-like protein 1 (Int1) (Gale et al., 1998; Staab et al., 2013), which binds to fibronectin, laminin, collagen I, and collagen IV (Khan et al., 2010); morphology-independent Eap1; Iff4; and a putative β-glucanase, Mp65 (de Bernardis et al., 2007; Fu et al., 2008; Li et al., 2007). In addition, these adhesins, mainly Als1 and Als3, are required for effective biofilm formation, particularly on the surfaces of medical devices such as catheters (Nobile et al., 2008).

3.2. Morphotype transition

C. albicans can grow as budding yeast, pseudohyphae, or hyphae *in vivo* (Staniszewska et al., 2013). The hyphal growth of *C. albicans* is promoted in an environment with a near neutral to alkaline pH (Sun et al., 2015), 5.5% CO_2, the presence of *N*-acetyl-d-glucosamine, serum, amino acids, and biotin and at 37–40 °C (Khan et al., 2010). The hyphal form is essential for tissue invasion, biofilm formation, and tissue damage, and results in mortality due to its ability for deep-seated infection, whereas the yeast form is more suitable for initial colonization, dissemination, and extravasation to target organs (Khan et al., 2010; Moran et al., 2012; Saville et al., 2003). Moreover, the hyphal form promotes penetration of the tissues, providing an escape from immune cells (Dalle et al., 2010; Lorenz et al., 2004). Two major signaling pathways regulate this multimorphism: (i) the Efg1 transcription factor-mediated cAMP-dependent pathway, and (ii) a MAPK pathway that activates the Cph1 transcription factor (Si et al., 2013). Farnesol, a quorum-sensing molecule, also regulates this transition (Lindsay et al., 2012).

3.3. Phenotype switching

Another factor involved in the adaptation of *C. albicans* to the host environment is its ability to undergo spontaneous and reversible phenotypic switching under stress conditions. These changes depend on the regulation of secreted aspartyl proteinases (Saps) and enhance fungal virulence. *C. albicans* colonies may be smooth, rough, star-shaped, stippled, hat-shaped, wrinkled, or fuzzy (Khan et al., 2010), and differ with respect to metabolism, biofilm formation ability, and, correspondingly, antifungal drug susceptibility (Morales et al., 2013). For instance, low oxygen conditions and catabolism of amino acids promotes wrinkled colony formation, and these wrinkled colonies alleviate redox stress (Bonhomme et al., 2011; Lindsay et al., 2014).

3.4. White, opaque, and gray cell switching

White and opaque cell types of *C. albicans* differ from each other with respect to metabolism, environmental adaptation, biofilm formation, and host interaction (Palková and Váchová, 2016; Xie et al., 2013). Epigenetic switching is mainly regulated by the mating type-like locus (*MTL*) (Si et al., 2013); however, expression of the master regulator Wor1, pH, and anaerobic conditions also affect switching to the opaque phenotype (Du and Huang, 2016; Sun et al., 2015). Both cell types could cause a lethal systemic infection; however, in contrast to white cells, opaque cells colonize the skin and do not secrete leukocyte chemoattractants (Palková and Váchová, 2016). Further, opaque cells are more resistant to phagocytosis by macrophages *in vitro* than are white cells. However, white cells are more virulent at higher temperatures and respond to pheromones by forming biofilms (Lin et al., 2013; Mallick et al., 2016); Efg1 is required for maintenance of this phenotype (Tao et al., 2014).

Tao et al. (2014) reported an additional *Candida* cell type, gray cells, which were first identified in *C. tropicalis* and then in *C. albicans*. These cells do not constitute a transitional form between white and opaque cells, and unlike the other cell types, their formation is independent of the two transcription factors Wor1 and Efg1. They also have unique carbohydrate metabolism and produce higher amounts of Saps (see below) than do white and opaque cells, and in general, they are most commonly isolated from cases of superficial infections (Tao et al., 2014). The fourth phenotypic state is described as a result of the gastrointestinally induced transition (GUT). Overexpression of Wor1 transcription factor on the white cells can induce this transition, and it is suggested that GUT forms promote commensalism in the gastrointestinal tract (Pande et al., 2013).

3.5. Secretion of enzymes

Following the invasion stage, fungi need to obtain nutrients and overcome host barriers for their further dissemination (Bennet, 2009). It is speculated that these microorganisms use phospholipases (PLs), lipases, and proteinases to this end (Mayer et al., 2013). There are four types of PLs: PLA, PLB, PLC, and PLD (Djordjevic, 2010). A comparative study of commensal and clinical *C. albicans* isolates revealed higher PL production in clinical isolates (Khan et al., 2010).

In addition to these enzymes, the most important virulence-associated extracellular hydrolytic proteins of *C. albicans* are the Saps (Gabrielli et al., 2016; Gropp et al., 2009; Puri et al., 2013). Different numbers of Saps are found in *C. tropicalis* (at least four; Sap1–4) (Zaugg et al., 2001), *C. parapsilosis* (Sap1 and Sap2) (Horváth et al., 2012), and *C. dubliniensis* (Sap1–3 and Sap6–10) (Jackson et al., 2009). In general, Saps damage the epithelial integrity and can digest albumin, hemoglobin, creatinine, collagen, laminin, fibronectin, mucin, interleukin-1β, and IgA proteins (Khan et al., 2010). Ten Saps (Sap1–10) have been identified in *C. albicans* to date. These enzymes are active at different pH values (i.e., pH 3.5 for Sap1–3; pH 5.0–7.0 for Sap4–6) and at different stages of infection: Sap1–3 play a role in early adherence,

invasion, and superficial infections; Sap8 is responsible for tissue penetration; and Sap6–9 are active at the early stages of hyphal growth (Khan et al., 2010). Although the Saps are considered to be important virulence factors, because of the difficulties in the establishment of relevant mutant strains, the specific roles of these enzymes in fungal pathogenesis remain controversial (Correia et al., 2010).

C. albicans also secretes the superoxide dismutases (SODs), SOD4 and SOD5. These enzymes deactivate ROS and contribute to the viability of fungi during co-culture with macrophages (Frohner et al., 2009). Additional enzymes such as metalloproteinase and serine protease are also thought to be important for the pathogenesis of *C. albicans* (Portela et al., 2010).

3.6. Biofilm formation

C. albicans is one of the most frequently isolated fungal species from catheter-associated biofilm infections (Rishpana and Kabbin, 2015) and invasive fungal infections associated with high morbidity and mortality rates (Cleary et al., 2016). The fungus can form biofilms on abiotic surfaces as well as in ocular (Sengupta et al., 2012), oral (Dongari-Bagtzoglou et al., 2009), intestinal (Ganguly and Mitchell, 2011), and vaginal (Harriott et al., 2010) environments. A mature biofilm is a three-dimensional structure that consists of yeast and hyphal forms in a polysaccharide/protein matrix with water channels (Fanning and Mitchell, 2012). The yeast form is essential for biofilm formation and biofilms that contain only hyphae can be readily disrupted (Baillie and Douglas, 1999).

Biofilm formation is tightly associated with the regulation of several protein and transcription factors, mainly Als3, Hwp1, Eap1, Bcr1, Ecm33, Sun41, Mkc1p, Gcn4 (Khan et al., 2010), Efg1, the kinase Yak1, and the zinc finger transcription factors Zap1 and Bcr1 (Kim and Sudbery, 2011). The current view is that a biofilm is an organized community controlled by quorum-sensing mechanisms. However, the role of the *C. albicans* quorum-sensing molecule farnesol in biofilm maturation has not been established. Farnesol appears to only affect yeast cells and prevents hyphal growth (Lu et al., 2014). Another quorum-sensing molecule, tyrosol, has been shown to have an inhibitory effect on adhesion and to promote fungal filamentation at low concentrations (Monteiro et al., 2015).

3.7. pH adaptation

C. albicans can adapt to different environmental conditions by expressing tissue-specific genes. One of the most important environmental conditions is pH. During its life cycle, *C. albicans* encounters different environmental pH conditions ranging from < 2 to > 10 (Du and Huang, 2016; Wilson et al., 2012) (Fig. 1). The fungus adapts to these conditions via the Rim101 signal transduction pathway, using the pH sensors Dfg16 and Rim21, which are found in the plasma membrane (Gomez-Raja and Davis, 2012). Rim101 also regulates two genes, *PHR1* and *PHR2*; *PHR1* becomes active during systemic infections and at pH $>$ 5.5 (optimum 5.8), whereas *PHR2* is active in vaginal infections and at pH $<$ 5.0 (optimum 3) (Du and Huang, 2016; Kováčová et al., 2015).

3.8. Nutrient and metal acquisition

Another challenge for the invading microbe is finding appropriate and sufficient nutrient sources. *C. albicans* prefers glucose to other nutrients, but this sugar is mainly unattainable to the pathogen, except when invading the bloodstream and the kidney (Gerich et al., 2001). During starvation, within the phagosome, *C. albicans* modifies its metabolism to the glyoxylate cycle. Enzymes such as isocitrate lyase and malate synthase are essential in this process (Lorenz and Fink, 2001; Piekarska et al., 2008); however, deficiency of these enzymes in *C. neoformans* (Rude et al., 2002) and *A. fumigatus* (Olivas et al., 2008) has no effect on fungal virulence. *C. albicans* becomes more virulent and resistant to stress when it uses carbon sources other than glucose (Ene et al., 2013). However, a combined evaluation of the independent and synergistic roles of nutrient source and infection site is required to gain a better understanding of the impact of the former on virulence.

Almost all organisms require iron for important cellular processes such as DNA synthesis, oxygen transport, drug metabolism, and cellular respiration and metabolism (Almeida et al., 2009). *C. albicans* obtains iron via at least three mechanisms: (i) hemoglobin uptake and degradation, (ii) siderophore uptake, and (iii) transferrin and ferritin uptake (Almeida et al., 2008, 2009). Iron promotes hyphal development in *C. albicans*, and iron metabolism is associated with the epithelial invasion, penetration, and development of systemic *C. albicans* infection (Potrykus et al., 2013; Xu et al., 2014a).

Although the importance of other metals such as zinc and copper is not as clearly established as that of iron, it is known that *C. albicans* secretes the zinc scavenger pH-regulated antigen 1 (Pra1), also called a "zincophore," to obtain zinc from host cells. Pra1 plays a role in *C. albicans* virulence by recruiting complement inhibitors to the fungal cell surface and binding complement factor C3a (Citiulo et al., 2012). *C. albicans* expresses the Ctr1 copper importer and the Crp1 copper efflux pump to obtain and export copper (as the other important metallic cofactor), respectively, both of which were shown to be essential for full fungal virulence in a murine model (Mackie et al., 2016).

3.9. Candidalysin

Fungal secondary metabolites, especially mycotoxins, have been largely investigated in air-borne or food-borne fungi such as *Aspergillus*, *Penicillium*, and *Fusarium* species (Ismaiel and Papenbrock, 2015). These metabolites are also assumed to play a role in fungal pathogenesis. However, there is little information about the mycotoxins produced by yeasts. The latest data pertaining to toxins produced by *Candida* species concerns the fungal cytolytic peptide Ece1-III, commonly known as "candidalysin," which is secreted by the hyphal form of *C. albicans* in the presence of epithelial cells. Strains lacking this toxin have been shown to be avirulent in animal models of mucosal infections and they do not cause damage to epithelial cells (Moyes et al., 2016).

3.10. Mating type

C. albicans is typically a diploid organism that had long been accepted to be asexual until an *MTL* locus was identified (Hull and Johnson, 1999). The majority of *C. albicans* isolates are heterozygous at the *MTL* locus with both the *MTL***a** and the *MTL*α idiomorph, whose key elements are a homeodomain and high-mobility group (HMG) domain transcription factors (**a**1 and **a**2), and an alpha box and homeodomain transcription factors (α1 and α2), respectively (Butler, 2010; Butler et al., 2009; Hull and Johnson, 1999). *C. albicans* has a heterothallic parasexual cycle that occurs when two diploid *C. albicans* cells (engineered to have deletions in the *MTL***a** or *MTL*α locus or induced to lose one or the other *MTL*-harboring chromosome) come together to form a tetraploid cell that eventually returns to the diploid state (or close to diploid) via concerted chromosome loss (Bennett and Johnson, 2003; Hull et al., 2000; Magee and Magee, 2000). In addition to the heterothallic mating that occurs between an **a**/**a** and α/α cell, *C. albicans* also undergoes homothallic mating under certain conditions (Alby and Bennett, 2011; Sun et al., 2016).

Although there is not much evidence to support a link between mating and virulence properties, considering the mating type, *MTL*-heterozygous strains were shown to be more virulent and have a competitive advantage over their spontaneous *MTL*-homozygous revertants due to the heterozygosity of both the *MTL* locus and the other genes at the *MTL*-harboring chromosome 5 (Lockhart et al., 2005; Wu et al., 2007).

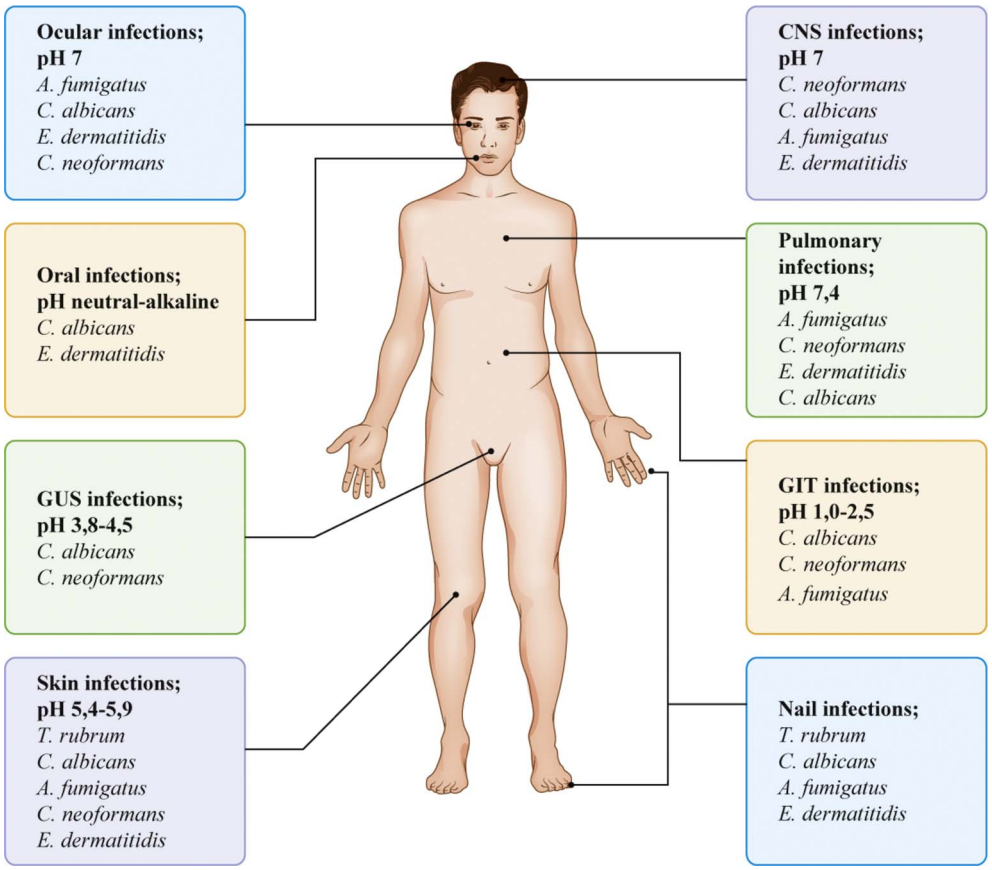

Fig. 1. Schematic distribution of five human fungal pathogens according to pH values of several anatomical and infection sites.

4. Cryptococcus neoformans

C. neoformans is one of the causative agents of fatal meningoencephalitis (Sudan et al., 2013). Since 2005, the genomes have been determined for all of the known species and varieties within the *Cryptococcus* pathogenic species complex, including *C. neoformans* var. *neoformans*, *C. neoformans* var. *grubii*, and five species within *C. gattii* (D'Souza et al., 2005, 2011; Farrer et al., 2015; Hagen et al., 2015; Janbon et al., 2014; Loftus et al., 2005).

4.1. Capsule

The capsule of *C. neoformans* plays a vital role in its virulence (Srikanta et al., 2014). Glucuronoxylomannan (GXM), glucuroxylomannogalactan (GXMGal), and mannoproteins are the main capsule components (Kwon-Chung et al., 2014; Vecchiarelli and Monari, 2012). The capsule is thought to protect the fungus from the host immune system, acting as a "shield;" however, many unanswered questions remain about its chemical structure and function (O'Meara and Alspaugh, 2012). Although it is poorly immunogenic, the capsule inhibits leukocyte migration from the bloodstream to the infection zone, suppresses T cell proliferation, induces interleukin-10 secretion, and reduces systemic inflammation. In addition, it is responsible for extrapulmonary dissemination of the fungus (Vecchiarelli and Monari, 2012) and the inactivation of complement and antibody responses (Bielska and May, 2016). Calcium concentration and the fungal cell wall components β-1,3-glucan and α-1,3-glucan also contribute to capsule formation (Kumar et al., 2011).

4.2. Capsule enlargement

The cryptococci can also respond to environmental changes by capsule enlargement, and this adaptive response is strongly related with the fungal cell cycle, particularly the G1 phase. Mutant strains with disrupted G1/S cyclin show a longer G1 phase and larger capsules. These strains also produce more extracellular vesicles compared to wild-type cells and are poorly internalized by phagocytic cells; however, they are avirulent at 37 °C and have relatively lower intracellular replication rates in murine macrophages (García-Rodas et al., 2014). Although elucidation of the molecular mechanisms and cellular changes related to such capsule enlargement requires further studies, it is clear the fungus invests a considerable important amount of its energy to this transition in order to survive under stress conditions (Trevijano-Contador et al., 2017).

4.3. Extracellular vesicles

Cell wall-associated structures known as extracellular vesicles (EVs) play a role in ferrying molecules to the extracellular space, and recent studies have shown that they are also associated with virulence, and are thus referred to as "virulence bags" (Rodrigues et al., 2008, 2014). The characteristics and potential roles of these vesicles in virulence have been analyzed for several pathogenic fungi such as *C. albicans*, *Histoplasma capsulatum*, and *Paracoccidioides brasiliensis* (Baltazar et al., 2016; Vallejo et al., 2012; Vargas et al., 2015).

These vesicles include important proteins such as laccase, urease, SOD, heat shock proteins, and ribosomal proteins (Rodrigues et al., 2008). EVs enhance the host immune response; although this may seem disadvantageous to the fungus, *C. neoformans* can survive in macrophages and remain "hidden" from the antifungal effects of the immune system (Bielska and May, 2016). In addition, production of EVs during infection allows the fungus to cross the blood-brain barrier (BBB) more efficiently (Huang et al., 2012).

4.4. Melanin

Melanin is mainly found in the fungal cell wall, which decreases the pore size on the cell and contributes to cell wall rigidity (Coelho and Casadevall, 2016). This characteristic has been suggested to be associated with the role of melanin in acquired drug resistance (especially in the case of resistance to amphotericin B and caspofungin) (Eisenman and Casadevall, 2012; Kwon-Chung et al., 2014). Melanin is also associated with EVs and may even be delivered to fungal cells distant from the producer cell via these vesicles (Coelho and Casadevall, 2016).

Many fungal species produce allomelanin [DHN (1,8-dihydroxynaphthalene)-melanin], although *C. neoformans* produces eumelanin [DOPA (3,4-dihydroxyphenylalanine)-melanin]. Eumelanins are black or brown in color and are derived from l-DOPA as a result of laccase activity (Sapmak et al., 2015). The l-DOPA pathway differs from the DHN pathway by occurring spontaneously after the initial enzymatic step, and melanin produced by this pathway contains nitrogen in addition to carbon and oxygen (Eisenman and Casadevall, 2012). *Cryptococcus* synthesizes eumelanin when substrates such as l-DOPA, monophenol, diphenol, and esculin are present (Almeida et al., 2015; Kwon-Chung et al., 2014). A positive correlation exists between laccase activity and the survival of *C. neoformans* in human cerebrospinal fluid (Sabiiti et al., 2014). The brain is enriched in DOPA, and thus *C. neoformans* may use it during brain infections to protect itself from oxidative damage. However, lack of laccase was shown to have no effect on fungal growth in the lung tissue (Liu et al., 2008). Moreover, mutants of two laccase genes, *LAC1* and *LAC2*, have melanin defects and decreased levels of melanin synthesis but without accompanying notable attenuation of virulence (Pukkila-Worley et al., 2005).

4.5. Thermotolerance

As almost all fungal virulence factors are a result of interactions with the fungus and other soil-associated organisms in the environment, thermotolerance must be considered in any discussion on fungal virulence. Birds can also be colonizers and transmitters of *C. neoformans* without signs of cryptococcosis (via the beaks, claws, and excretas, for example), and studies with avian macrophages revealed that a higher avian body temperature (42 °C) suppresses fungal proliferation in macrophages. Johnston et al. (2016) reported that this thermotolerance facilitates the external growth of the fungi but it is not sufficient for intracellular survival in macrophages. Moreover, in their experiments, only a few cryptococci could escape and survived by vomocytosis or cell enlargement, and shifting the environment to lower temperatures allowed for intracellular fungal proliferation. *C. neoformans* and *C. gattii* can survive and grow at 37 °C, although this tolerance requires the protein phosphatase calcineurin (Kozubowski et al., 2011). Calcineurin is an important regulator of calcium homeostasis in many macro- and micro-organisms. Besides its role in enabling fungal survival at elevated temperatures and alkaline pH, calcineurin also regulates the integrity of the cell wall and cell membrane (Chen et al., 2011; Juvvadi et al., 2017; Lev et al., 2012). However, there are still some gaps in the understanding of its fungal substrates and activation mechanisms (Park et al., 2016). In addition, the loss of Sch9 protein kinases and overexpression of Hsf1 protein increase *C. neoformans* thermotolerance (Yang et al., 2017).

4.6. Urease activity

Undoubtedly, several enzymes play crucial roles in fungal pathogenesis. For instance, 99.6% of *C. neoformans* isolates possess nickel-requiring urease activity (Zimmer and Roberts, 1979). Urease enables the utilization of urea as a nutrient source, which allows the fungus to survive within microcapillary beds (Feder et al., 2015), perhaps as a result of the local production of ammonia. Ammonia may exert mechanical effects on the endothelium to change the shape of microvessels. It may also affect endothelial tight junctions by promoting cell toxicity, leading to the opening of junctions, or it might compromise BBB integrity (Olszewski et al., 2004). During pulmonary infections, urease promotes the accumulation of mature dendritic cells in the lung and facilitates fungal dissemination (Kwon-Chung et al., 2014). Murine experiments have demonstrated that urease triggers a Th2 immune response rather than the more effective Th1 response to cryptococcal infections (Singh et al., 2013). However, urease-deficient strains can also cause disseminated infections and penetrate the BBB (Cox et al., 2000). Although urease plays a role in fungal transmission through the BBB, its effect on cell survival in the brain remains unknown (Morrow and Fraser, 2013; Singh et al., 2013).

4.7. BBB

Transmission across the BBB is crucial for the development of cryptococcal infection in the central nervous system, although it may be more related with infection mechanisms than virulence factors. Nevertheless, it is unclear whether BBB penetration is achieved by free fungal cells or by fungi that have been phagocytosed by mononuclear phagocytes. Fungi can cross the BBB paracellularly, taking advantage of damage to the brain endothelium and BBB integrity, the latter caused by enzymes such as urease (Sorrell et al., 2016), serine protease (Xu et al., 2014b), laccase (Qiu et al., 2012), PLB (Maruvada et al., 2012), and secreted fungal metalloprotease (Mpr1) (Vu et al., 2014). Another possibility is a transcellular mechanism (transcytosis), which requires adhesion, internalization, and migration steps (Sabiiti and May, 2012). Some evidence has been put forward to indicate that the *Cryptococcus*/monocyte interaction leads to crossing of the BBB by a “Trojan horse” mechanism. Sorrell et al. (2016) reported that cryptococci migrate between Th1 cells, with the integrity of human brain endothelial cells preserved during the process. Vomocytosis, or phagosomal extrusion, is a non-lytic mechanism that is not entirely understood but is thought to facilitate the dissemination and deposition of fungal cells in macrophages, thereby facilitating the “Trojan horse” mechanism by enabling fungal egress from host macrophages (Bielska and May, 2016).

4.8. Titan cells

During cryptococcal infection, the most important morphological change of the fungus involves “titan cell” formation. In normal circumstances, the *C. neoformans* cell size is 4–8 μm, but titan/giant cells can reach up to 100 μm (Zaragoza and Nielsen, 2013). Because titan cells cannot be phagocytosed, they may also prevent the phagocytosis of “normal” *C. neoformans* cells in their vicinity, especially at early stages of infection (Crabtree et al., 2012; Okagaki and Nielsen, 2012). Moreover, although titan cells cannot pass through the brain tissue, they facilitate the transmission of “normal” *C. neoformans* cells from the lung to other tissues. Titan cells are also resistant to oxidative and nitrosative stresses; they hamper infection clearance and may play a major role in latent infection (Zaragoza et al., 2010). Despite the importance of these cells for the virulence of *C. neoformans*, it has thus far been difficult to investigate the parameters affecting their formation. According to the latest reports, titan cell formation depends on both host and fungal factors such as certain lipids, mating type (García-Barbazán et al., 2016), and Plb1 (Evans et al., 2015).

4.9. Mannitol

In addition to fungal enzymes, some metabolic molecules such as mannitol may contribute to fungal pathogenesis. A correlation between increased hexitol (d-mannitol) production and meningoencephalitis has been reported (Wong et al., 1990). Although *C. neoformans* can synthesize mannitol both *in vitro* and *in vivo*, its role as a metabolite is not entirely understood. Nevertheless, increased osmotic pressure due to mannitol causes edema in the brain, which might protect the fungus

from oxidative damage (Guimarães et al., 2010). In addition, strains that produce lower amounts of mannitol are more sensitive to heat and osmotic stresses than those producing higher amounts (Chaturvedi et al., 1996). Guimarães et al. (2010) evaluated the *in vivo* and *in vitro* utilization of mannitol and glucose as a carbon source by *C. neoformans*, which revealed the capacity of the carbohydrate source and concentration to modify the expression of a major virulence factor of *C. neoformans* (Guimarães et al., 2010). This might be associated with the intracellular survival-promoting effect of mannitol (García-Rodas and Zaragoza, 2012). Nevertheless, there is need for more evidence to establish mannitol as a virulence factor for *C. neoformans*.

4.10. Inositol

Another factor associated with cryptococcal dissemination to the brain is the sugar inositol. Inositol is a major osmolyte in the brains of humans and other animals, and can be utilized as a nutrient by *Cryptococcus* species. It promotes the association between fungi and human brain microvascular endothelial cells (HBMECs), and a stronger association can cause increased transmigration (Liu et al., 2013). Moreover, inositol plays an important role in fungal phospholipid production, which might help to explain its observed effect on HBMECs (Liu et al., 2013). Inositol directly affects fungal cells by enhancing BBB traversal (Liu et al., 2013), and appears to exert an indirect effect on capsule production, given the detection of altered capsule structures when the inositol transporters Itr1a and Itr3c are mutated (Liu et al., 2014).

4.11. Biofilm formation

Advances in biomedical device technology have been accompanied by a stark increase in the prevalence of biofilm-associated infections. *C. neoformans* has been reported to form biofilms on polystyrene surfaces, ventriculoatrial shunts, ventriculoperitoneal shunt catheters, and cardiac valves (Gullo et al., 2013; Martinez and Casadevall, 2015). Cryptococcal biofilms are resistant to fluconazole and voriconazole; they are also more resistant to amphotericin B, caspofungin, and oxidative stress than planktonic cells (Martinez and Casadevall, 2015). Drug resistance associated with biofilm formation is a complex phenomenon because it is also associated with other fungal factors such as capsule formation (especially GXM) and melanin production. Because of these additional effects, several factors (i.e., pH, temperature, and carbon source) can affect biofilm formation (Martinez and Casadevall, 2007).

The characteristics of *C. neoformans* biofilms vary depending on the fungal serotype. For instance, *C. neoformans* serotype A strains form more durable biofilms that are harder to disperse than those formed by serotype B strains, even after co-incubation with *Acinetobacter baumannii* (Abdulkareem et al., 2015). *C. neoformans* interacts with many soil micro- and macro-organisms present in the environment, and this survival strategy may help the fungus to overcome harsh conditions, potentially accounting for the higher prevalence of serotype A strains in the environment (Abdulkareem et al., 2015).

4.12. Phenotypic switching

Similar to *C. albicans*, *C. neoformans* can also undergo phenotypic switching in which the colony morphology of serotypes A, B, and D strains differs from that of the smooth parent variant (e.g., wrinkled, mucoid, or serrated) (Martinez et al., 2008; Palková and Váchová, 2016). These variants differ with respect to their capsular polysaccharide. Smooth cells form stronger biofilms (Martinez et al., 2008), and because they have smaller capsules, these cells can more efficiently cross the BBB (Jain et al., 2006; Sabiiti and May, 2012). However, cells from wrinkled colonies are more virulent, with an enlarged capsule (Fries et al., 1999). This switching ability changes the immunological host response by altering macrophage activation (i.e., shift to a T17-type T-cell response) (Guerrero et al., 2010). In addition, the IL-10 response to these variants differs, and switching may be associated with persistent *C. neoformans* infections and death (Guerrero and Fries, 2008).

4.13. Nutrient acquisition

Once the pathogen is phagocytosed, one of the main challenges that it encounters is nutrient acquisition. *C. neoformans* is able to switch its nutrient uptake mechanism from glycolysis to gluconeogenesis (Derengowski et al., 2013). In the phagosome, *C. neoformans* can damage the phagosomal membrane to access cytoplasmic nutrients (Coelho et al., 2014). *C. neoformans* may also obtain nutrients through autophagy (Nicola et al., 2012).

4.14. Iron and copper utilization

Similar to many other pathogenic microorganisms, *C. neoformans* has to obtain iron from the host's iron-binding proteins. *Cryptococcus* possesses a number of iron uptake systems such as ferric reductase (laccase) and a high-affinity ferroxidase and permease complex, in addition to siderophore utilization (Coelho et al., 2014). Melanin is also involved in iron reduction. Iron utilization is related to several crucial processes mediating the virulence and infectivity of the fungus, such as melanin production, capsule formation, glycolysis, ergosterol synthesis, and inositol utilization (Kronstad et al., 2012). In addition, mitochondrial iron homeostasis is essential for an efficient response to oxidative stress (Ingavale et al., 2008). Reductive iron uptake is also required for *C. neoformans* dissemination to the brain (Saikia et al., 2014) and antifungal drug detoxification (Kim et al., 2012).

Copper, one of the metallic cofactors, plays an important role in the pathogenesis of *C. neoformans* (Coelho et al., 2014). Copper is required for the activity of some crucial enzymes, including laccase and SOD (Mauch et al., 2013); however, accumulation of this metal is toxic to *C. neoformans*. Thus, when the host activates an antimicrobial copper response (copper poisoning), the fungus inhibits accumulation of copper using copper detoxifiers by decreasing expression of the copper importer (Ding et al., 2013).

4.15. Mating type

The varieties of *C. neoformans* and its sibling species *C. gattii* have well-defined heterothallic sexual cycles, which are observed when *MAT***a** and *MAT*α strains mate under a variety of environmental conditions (Kwon-Chung, 1976a, 1976b; McClelland et al., 2004; Nielsen et al., 2003). The sexual reproduction process is governed by an unusually large *MAT* locus, which spans more than 100 kb. This locus contains more than 20 genes, including a homeodomain transcription factor gene and pheromone and pheromone receptor genes, as well as mating and meiosis-related genes and genes with as yet unknown functions (Fraser et al., 2004; Lengeler et al., 2002; Zhang et al., 2015). The α mating type predominates in environmental and clinical isolates of *C. neoformans* and *C. gattii* (Kwon-Chung and Bennett, 1978; Litvintseva et al., 2003; Nielsen and Heitman, 2007).

In certain genetic backgrounds of *Cryptococcus*, the α mating type showed greater virulence using congenic strains (Kwon-Chung et al., 1992), but congenic strains of other backgrounds demonstrate equal virulence (Nielsen et al., 2005a, 2005b; Zhai et al., 2013; Zhu et al., 2013). Therefore, the variable results obtained show that the role played by mating type in the virulence of *C. neoformans* and *C. gattii* can be strain-dependent.

5. Trichophyton rubrum

T. rubrum is the primary causative agent of tinea pedis and onychomycosis, and is responsible for 69.5% of all *Trichophyton* infections

(Hube et al., 2015; Ilkit and Durdu, 2015). *T. rubrum* displays pronounced keratinase activity at normal body temperature and the pH of the skin, which has been referred to as "anthropozation" (Nenoff et al., 2014). Thus, this fungus is well adapted to the human host, and its infections tend to be chronic with a potential to spread to other anatomical sites (Ilkit and Durdu, 2015). Carbohydrate-specific adhesins are expressed on the surface of its microconidia, which are required for fungal adhesion to the epithelial cells. In addition to adhesins, secreted proteases may also participate in the adhesion process (Monod et al., 2005).

5.1. Keratinases

Because dermatophytes are keratinophilic and keratinolytic, keratinases are among the most well studied enzymes in this fungal group. Keratinases are secreted as multiple serine and metallo-endoproteases (Sharma et al., 2012). The fungi also secrete multiple sets of proteases. However, only some are highly expressed and play a role in the fungus-keratinocyte interaction (Achterman and White, 2012). Before utilization of the tissue keratin, fungi have to destroy disulfide bridges and the integrity of the tissue. To do this, they secrete sulfites via efflux pumps encoded by the *SSU1* gene (Grumbt et al., 2013). Therefore, dermatophytic fungi need to upregulate several enzymes such as isocitrate lyase, malate synthase, and citrate synthase to survive in keratinized tissue (Peres et al., 2016).

5.2. Hyphal development

Hyphal development occurs after adhesion to the stratum corneum, whereupon the fungus moves towards the deeper layer of the stratum corneum (Brasch, 2010). This progression may trigger further tissue damage and inflammation, and involves several secondary metabolites. Hemolysin, a cytotoxic exotoxin, may be advantageous for *T. rubrum* during infection, particularly during bacteria-dermatophyte interactions such as in erysipelas and tinea pedis (Döğen et al., 2015).

5.3. Secondary metabolites

T. rubrum produces a lipophilic toxin, xanthomegnin, and several aflatoxin-like toxins, which are thought to play a role in fungal pathogenesis because of their immunosuppressive characteristics (Hube et al., 2015; Kandemir et al., 2015). *In vitro* laccase activity was also detected in *T. rubrum*, but the link between the presence of melanin and virulence has not been unequivocally established (Youngchim et al., 2011). Dermatophytes also produce LysM domain-associated proteins, which are thought to be important for latent infection as they mask chitin in the fungal cell wall and prevent the recognition of fungi by the human immune system (Martinez et al., 2012).

5.4. Biofilms

T. rubrum can produce biofilms (Costa-Orlandi et al., 2014), which hinders the penetration of antifungal agents (Gupta et al., 2016). In addition to biofilms, the fungus can use efflux pumps to extrude drugs, which may cause further delays in the treatment response.

6. Exophiala dermatitidis

Black yeasts show polyextremophilic features and, in general, expression of some specific gene families (i.e., alcohol and aldehyde dehydrogenases, membrane transporter proteins, and cytochrome P450) is thought to be essential for their survival in extreme conditions (Moreno et al., Unpublished data; Teixeira et al., 2017). Most disseminated black yeast infections are caused by *Exophiala* species, mainly the thermophilic species *Exophiala* (*Wangiella*) *dermatitidis*.

6.1. Melanin and carotene

Melanin is deposited in the cell wall of melanized fungi and plays an important role in virulence and pathogenicity; this is the most remarkable characteristic of *E. dermatitidis* and of black yeasts in general (Chen et al., 2014; Paolo et al., 2006; Robertson et al., 2012; Szaniszlo, 2006). *In vivo* studies also showed that melanin-deficient *E. dermatitidis* mutants were significantly less virulent than the wild type (Dixon et al., 1987). In addition to its main function in irradiation protection, melanin allows the fungus to escape phagocytosis and provides protection against free radicals. In the case of a high H_2O_2 concentration, yeast conversion is promoted and hyaline structures are observed as a result of loss of melanization (Song et al., Unpublished data). Besides melanin, black yeasts and their filamentous relatives synthesize carotenoids (Chen et al., 2014). The mechanism of carotenoid action more likely involves the shielding of sensitive molecules or organelles rather than the neutralization of harmful oxidants (Chen et al., 2014).

6.2. Chitin synthases

Together with β-1-3-linked glucan, chitin plays an important role in cellular development, structural morphogenesis, spore formation, and the maintenance of cell wall integrity (Szaniszlo, 2006). *E. dermatitidis* has at least seven chitin synthase enzymes, but unlike the other six enzymes, WdChs5p (Class V) is required for fungal growth at 37 °C and mutants of this enzyme result in hyperpigmentation, abnormal morphologies, a smaller colony structure, and loss of cell wall integrity (Abramczyk et al., 2009). Furthermore, the transition between growth phases does not exist in Class II *chs1* mutant *E. dermatitidis* strains (Zheng et al., 2006).

6.3. Presence of yeast-like phases

Because of its ability to form different morphotypes, *E. dermatitidis* can readily adapt to changing environmental conditions. For instance, the fungi can grow in yeast form in hydrophilic conditions, whereas hyphal growth occurs in more hydrophobic conditions. This survival strategy also results in hematogenous dissemination in the human host, which may occur in different infection settings (de Hoog, 1993). The majority of hematogenously disseminated black yeast infections are caused by *Exophiala* species, which are able to produce yeast-like cells (Abramczyk et al., 2009; Nucci et al., 2002). Infections caused by *Exophiala* species are usually restricted to the skin and soft tissues. The fungus usually causes a localized infection, involving the production of different hyphal growth morphotypes (de Hoog et al., 2007).

The transmission routes of *Exophiala* species have been investigated to better understand their biology and for the development of prevention and treatment strategies, especially for *E. dermatitidis* infections. *E. dermatitidis* is suggested to be mainly acquired by inhalation (Zupančič et al., 2016), ingestion of contaminated natural spring water (Tesei et al., 2015), or skin trauma (Lian and de Hoog, 2010). However, some extraordinary cases have been reported, such as an outbreak of *E. dermatitidis* central nervous system infections caused by administration of contaminated intravenous drugs (CDC, 2002; Perfect, 2012; Vasquez et al., 2016). *E. dermatitidis* can be found in diverse human-made environments where many people come into contact [i.e., railway sleepers (Gümral et al., 2014), dishwashers (Zupančič et al., 2016), and bath facilities (Gostinčar et al., 2011)], and it can colonize the lungs of patients with cystic fibrosis. All of these data indicate that human opportunism by these fungi is likely accidental and a secondary result of overcoming the stresses of extreme conditions (Gostinčar et al., Unpublished data). The establishment of infection depends on the inoculum amount and the effort required to enter the body. Once the fungus enters, then fungal proliferation readily occurs.

6.4. Adhesion and hydrophobicity

Most *Exophiala* species exhibit strong morphological plasticity in response to environmental conditions, and produce phialides with sticky balls of small conidia that may mediate adherence. Establishment of a disease can be achieved by adhesion to target cells. The relative cellular hydrophobicity may enhance this adhesion step, which allows the fungi to differentiate into muriform cells that are resistant to host immune system components (de Hoog et al., 2007; Seyedmousavi et al., 2014).

6.5. Assimilation of aromatic hydrocarbons

Numerous species of black yeasts of the Chaetothyriales can be isolated from odd environments such as those polluted with toxic hydrocarbons. These species show a remarkable association with sites containing monoaromatic hydrocarbons and may have a competitive advantage when these compounds are present (Seyedmousavi et al., 2014). The ability to assimilate multiple compounds is potentially involved in the virulence of black yeasts. This has been surmised based on the structural similarity of assimilated compounds with neurotransmitters, possibly explaining the predilection of this fungus for nervous tissue infection (Prenafeta-Boldú et al., 2006; Zhao et al., 2010).

6.6. Production of secondary metabolites

Black yeasts produce extracellular acidic or alkaline metabolites and siderophores that may also act as virulence factors (de Hoog, 1993). These secondary metabolites are also essential for fungal colonization of ecological niches, and *E. dermatitidis* has potential gene clusters for secondary metabolites, including polyketides (PKSI and PKSIII), nonribozomal peptides (NRPS), and terpenes (Teixeira et al., 2017). *E. dermatitidis*, when disseminated, shows marked neurotropism (Li et al., 2011); in contrast to *Aspergillus* and Mucorales, in which brain infections are secondary, the brain is the primary site of *E. dermatitidis* infection (Horrè and de Hoog, 1999). This may be caused by a slightly higher level of free iron in the central nervous system than in the serum, and the ability of *E. dermatitidis* to use the siderophores to gain iron (Chen et al., 2014).

7. Conclusion

Overall, this review illustrates that some of the putative virulence factors that suppress host immunity and enhance the infectivity of fungi are unique and may act differently among the five pathogenic fungi reviewed here that have been extensively studied to date. The ability to survive and cause disease at different sites of the human body undoubtedly requires the acquisition of special abilities, as observed in these five fungi. Although thermotolerance is the greatest advantageous trait of these fungi, producing different types of cells and enzymes strengthens their abilities. Depending on the species, fungi can be transmitted or disseminated in yeast form but can also penetrate tissues and escape predators in hyphal form. To obtain essential elements such as iron, fungi use either their own siderophores as in *E. dermatitidis* or other mechanisms as in *C. albicans*, *C. neoformans*, and *A. fumigatus*. Other than the essential enzymes required for all fungi, producing some special enzymes can facilitate adaptation to new conditions such as keratinases for *T. rubrum* and urease and laccase for *C. neoformans*. Escaping from the human immune system cells is one of the key challenges for fungi, and they have several defense or attack mechanisms to overcome this. Muriform cells and melanin provide this protection in *E. dermatitidis*, whereas similar effects are conferred by the switching ability and SODs in *C. albicans*; melanin, mycotoxins, and the hydrophobin RodA in *A. fumigatus*; and vomocytosis, switching, capsule, melanin, and EVs in *C. neoformans*.

In *A. fumigatus*, fungal secondary metabolites also reduce adherence. Identification of the molecular mechanisms underlying adherence has revealed protein-based structures for *C. albicans*, whereas an important role of the fungal carbohydrate components of the cell wall and ECM has been demonstrated in *A. fumigatus*. In *C. neoformans*, production of a polysaccharide capsule, and the soluble extracellular constituents produced in response to iron limitation are suggested to be the dominant virulence factors. Among these five fungal species, only *E. dermatitidis* shows a unique polyextremophilic character. Although virulence factors are thought to be consequences of the fungal survival efforts rather than adaptations for causing disease in humans, understanding these factors will further help to develop new strategies for the prevention and treatment of fungal infections.

Conflict of interest

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