Review Article

Fungal Dimorphism and Virulence: Molecular Mechanisms for Temperature Adaptation, Immune Evasion, and In Vivo Survival

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Received 18 November 2016; Accepted 12 April 2017; Published 23 May 2017

Academic Editor: Anamélia L. Bocca

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The thermally dimorphic fungi are a unique group of fungi within the Ascomycota phylum that respond to shifts in temperature by converting between hyphae (22–25°C) and yeast (37°C). This morphologic switch, known as the phase transition, defines the biology and lifestyle of these fungi. The conversion to yeast within healthy and immunocompromised mammalian hosts is essential for virulence. In the yeast phase, the thermally dimorphic fungi upregulate genes involved with subverting host immune defenses. This review highlights the molecular mechanisms governing the phase transition and recent advances in how the phase transition promotes infection.

1. Introduction

The ability for fungi to switch between different morphologic forms is widespread throughout the fungal kingdom and is a fundamental part of their biology. A small subset of fungi within the Ascomycota phylum is considered dimorphic, which refers to capacity to convert between two specific morphologic forms, yeast and hyphae. These fungi are capable of infecting mammals, plants, and insects, and can be subdivided into thermal and nonthermal dimorphic fungi [1]. Thermally dimorphic fungi infect humans and other mammals such as dogs, cats, armadillos, and rodents (Table 1) [2–8]. The thermally dimorphic fungi are unique among fungal pathogens because they can infect humans with normal and impaired immune defenses. This includes the etiologic agents for blastomycosis, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, and sporotrichosis. In contrast, penicilliosis and emmonsiosis occur in persons with long-standing HIV infection that has progressed to AIDS (CD4+ T lymphocytes ≤ 200 cells/mm³) or have impaired cell-mediated immunity for other reasons (e.g., solid organ transplant) [9–11]. Nonthermal dimorphic fungi can also cause human infection (e.g., Malassezia furfur) [12] but are more typically phytopathogenic or entomopathogenic. For example, Ophiostoma novo-ulmi, the etiologic agent of Dutch elm disease, has destroyed millions of elm trees in Europe and United States [13]. The “zombie ant” fungus, Ophiocordyceps unilateralis, secretes metabolites to alter the behavior of infected ants [14]. This review will focus on how the morphologic switch between hyphae and yeast contributes to virulence with an emphasis on thermally dimorphic fungi relevant to human health.

2. The Phase Transition

The reversible morphologic transition between hyphae and yeast, which is known as the phase transition, is fundamental feature of the biology and lifestyle of the dimorphic fungi [1]. In the soil (22–25°C), these fungi grow as septate hyphae that produce conidia. Disruption of soil by human activities such as construction or natural disasters can aerosolize conidia and hyphal fragments. When inhaled into the warm lungs of a mammalian host (37°C), these infectious propagules convert into pathogenic yeast (or spherules for Coccidioides) to cause pneumonia [1]. Once infection is established in the
lungs, the yeast (or spherules) can disseminate to other organs such as the skin, bone, or brain.

Although temperature is the predominate stimulus that influences the phase transition—hyphae at 22–25°C and yeast at 37°C, additional stimuli that impact the dimorphic switch include carbon dioxide (CO₂) tension, exogenous cysteine, and estradiol. Elevated CO₂ tension (5% CO₂) is required for the arthroconidia of Coccidioides spp. to germinate into spherules at 37°C and for optional growth of Histoplasma capsulatum yeast [15, 16]. In the human lung, CO₂ tension is approximately 150-fold higher than ambient air, which provides an optimal amount of CO₂ for phase transition [17]. In response to an upshift in temperature, mitochondrial respiration ceases in hyphae at 22–25°C and yeast at 37°C. In the presence of 17β-estradiol by humans influences the morphologic shift and growth of Coccidioides and Paracoccidioides, which in turn, modulates the severity of infection in women. In the presence of 17β-estradiol, the growth of Coccidioides spherules at 37°C is accelerated, which may explain the increased risk for disseminated coccidioidomycosis in pregnant women [20, 21]. Moreover, in vitro analysis has demonstrated that Coccidioides spherules exhibit saturable binding of 17β-estradiol [21]. In contrast to Coccidioides, the morphologic switch from hyphae or conidia to yeast in Paracoccidioides is blocked by 17β-estradiol [22, 23]. In a murine model of pulmonary infection, the conversion of conidia to yeast is impaired in female, but not in male mice [24]. In humans, the incidence of paracoccidioidomycosis is 11–30-fold higher in adult males than in adult females despite similar frequency of Paracoccidioides exposure. Prior to puberty, the male-to-female ratio is 1 : 1 [25].

These observations have prompted investigation to the mechanisms by which estradiol and gender influence fungal development and the host response. Gene expression microarray analysis of P. brasiliensis strain Pb01 demonstrated that impaired conversion to yeast at 37°C in the presence of 17β-estradiol reduced the transcription of genes involved with cell signaling (small GTPase RhoA, palmitoyltransferase), heat shock (HSP40, HSP70, and HSP90), chitin synthesis (chitin synthase), and glucan remodeling (β-1,3-glucan synthase, α-1,3-glucan synthase) [25]. When stimulated with paracoccin, a lectin-binding protein with chitinase activity, female mice exhibit a stronger Th1 cytokine response with increased production of tumor necrosis factor alpha (TNF-α), interferon gamma (INF-γ), and interleukin 12 (IL-12), along with increased macrophage fungicidal activity when compared to male mice [26]. Following oophorectomy and treatment with testosterone, the cytokine response shifted from Th1 to Th2 in female mice. Castration of male mice coupled with estradiol therapy favored a Th1 cytokine response instead of a Th2 cytokine response [26]. Collectively, these findings highlight the importance of sex steroid hormones and gender on fungal development and host susceptibility.

3. Yeast-Phase Virulence Factors and Subversion of Host Immune Defenses

Once inhaled into the lungs, conidia are ingested by macrophages, where they germinate into yeast (or spherules for Coccidioides) and replicate. Histoplasma capsulatum, Coccidioides immitis and posadasii, Sporothrix schenckii, Paracoccidioides brasiliensis and lutzii, and Talaromyces marneffi replicate inside and outside of innate immune cells [27–31]. Traditionally, Blastomyces spp. were thought to be exclusively extracellular; however, recent research demonstrates that B. dermatitidis conidia ingested by macrophages survive and convert to yeast [32].

During the phase transition, the thermally dimorphic fungi upregulate yeast-phase specific genes including Blastomyces adhesion-1 (BAD-1), calcium-binding protein-1 (CBP1), yeast-phase specific-3 (YPS3), and the surface outer wall glycoprotein (SOWgp) to actively subvert host immune defenses. B. dermatitidis and B. gilchristii express BAD1 (formerly WI-1), a 120kDa secreted, multifunctional protein serves as an adhesion and immune evasin [33–38]. Secreted BAD1 binds back to the yeast cell surface via interactions with chitin and also remains soluble in the extracellular milieu [33–35]. Cell surface-bound BAD1 binds yeast to host cells via complement receptors (CR3, CD14) and heparan sulfate to promote yeast cell adhesion to host cells. BAD-1 bound to the yeast cell surface inhibits production of TNF-α by macrophages and neutrophils in a transforming growth factor-β (TGF-β) dependent manner [33, 36–38]. In contrast, soluble BAD-1 blocks TNF-α production independent of TGF-β [36]. TNF-α is a critical cytokine for proper host defense against the dimorphic fungi. Neutralization of TNF-α in a murine model of infection results in progressive pulmonary blastomycosis [37]. Moreover, in 2008, the Food and Drug Administration (FDA) issued a warning of increased risk for histoplasmosis, blastomycosis, and coccidioidomycosis for persons on TNF-α inhibitors for treatment of autoimmune disorders (e.g., rheumatoid arthritis and Crohn’s disease) [39]. In addition to affecting TNF-α production, BAD1 also impairs the adaptive immune response by inhibiting the activation of CD4+ T lymphocytes, which decreases IL-17 and INF-γ production [33]. The adhesion and immunomodulatory activities of BAD1 are essential for Blastomyces pathogenesis. Deletion of BAD1 renders Blastomyces yeast avirulent in murine model of pulmonary infection [40]. In addition to BAD1, Blastomyces dermatitidis...
secretes a dipeptidyl-peptidase IVA (DppIVA) to modulate host immunity. DppIV is a serine protease that cleaves GM-CSF, a potent cytokine that activates macrophages and neutrophils to kill fungi [41]. Silencing DppIVA by RNA interference (RNAi) reduces survival of B. dermatitidis yeast cocultured with GM-CSF-activated macrophages and neutrophils [41]. Moreover, DppIVA-RNAi strains have attenuated virulence during pulmonary infection [41]. In contrast to B. dermatitidis, H. capsulatum DppIVA is not detected extracellularly and does not contribute to virulence [42, 43].

Analogous to BAD1, Coccidioides SOWgp is localized to the spherule cell surface and an important virulence factor. SOWgp facilitates binding of spherules to host extracellular matrix (ECM) proteins including laminin, fibronectin, and collagen [44]. Deletion of SOWgp (SOWgpA) in Coccidioides impairs spherule adherence to ECM proteins and results in attenuated virulence in a murine model of pulmonary infection [44].

In H. capsulatum, CBP1 is a secreted virulence factor that promotes intracellular replication of yeast [45, 46]. CBP1 binds calcium, exists as homodimer, is resistant to protease degradation, and is structurally related to a group of membrane lipid-binding proteins known as saposins [47, 48]. CBP1 secreted by intracellular H. capsulatum yeast induces macrophage apoptosis and lysis by inducing transcription of host cell caspases, transcription factors (NUPR1I/p8, TRB3), and genes involved with endoplasmic reticulum (ER) stress [46]. Thus, macrophage lysis is an active process directed by the fungus and not due to high intracellular fungal burden. Similar to BAD1, CBP1 is an essential virulence factor. CBP1 null mutants (CBP1Δ) are unable to induce macrophage apoptosis and are avirulent in murine model of pulmonary infection [45, 46]. In addition to CBP1, H. capsulatum secretes YPS3, which binds back to chitin in the yeast cell wall and facilitates extrapulmonary dissemination to the liver and spleen [49].

During the morphologic switch from hyphae to yeast or conidia to yeast, dimorphic fungi undergo extensive remodeling of the cell wall including glucon composition. Reorganization of glucon content has the potential to impede recognition of pathogen-associated molecular patterns (PAMPs) by host immune cells. During the morphologic switch, the amount of β-(1,3)-glucan in the cell wall of Blastomyces and Paracoccidioides declines from ~40% in hyphae to ~5% in yeast [50, 51]. The reduction of β-(1,3)-glucan in the yeast cell wall may limit its recognition by dectin-1 on innate immune cells and mannose-binding lectins [17, 52]. In contrast, H. capsulatum does not reduce β-(1,3)-glucan in yeast cells, but rather it uses α-(1,3)-glucan as a “shield” to block dectin-1 recognition of β-(1,3)-glucan [53]. Thus, the dimorphic fungi utilize multiple strategies including secreted virulence factors and modification of the yeast cell wall to subvert host immune defenses to establish infection including in persons with intact immune systems.

The ability of thermally dimorphic fungi to subvert host immune defenses is not 100% effective. The host can mount an immune response to halt the progression of infection. Epidemiologic studies have demonstrated that ~50% of persons exposed to Blastomyces spp. develop symptomatic infection, whereas ~50% have asymptomatic or subclinical infection [54, 55]. Similarly, inhalation of Histoplasma capsulatum, Coccidioides spp., and Paracoccidioides spp. results in symptomatic infection in <10%, 33–50%, and <5% of healthy persons, respectively [56–58]. Intact innate and adaptive immune defenses along with the ability to “walk-off” yeast in granulomas are critical for host defense against infection. Following the conversion of conidia to yeast, dendritic cells and macrophages interact with and engulf yeast cells. Gene expression analysis of dendritic cells that have phagocytosed P. brasiliensis yeast demonstrated upregulation of transcripts involved with generating a protective immune response including TNF-α, IL-12, and chemokines (CCL22, CCL27, and CXCL10) [59]. In addition, the dectin-1 receptor was upregulated, which induces phagocytosis, generation of reactive oxygen species, and proinflammatory cytokines and chemokines in response to binding β-(1,3)-glucan [59, 60]. Chemokines promote leukocyte migration to sites of infection [59]. Similarly, macrophages infected with P. brasiliensis also induce a proinflammatory response with upregulation of TNF-α, chemokines (CCL21, CCL22, CXCL4, CXCL11, and CXCL14), and kinases (IRAK2) [61]. These findings highlight the ability of the immune defenses to limit the impact of fungal virulence factors.

4. Regulation of the Phase Transition

The transition from hyphae or conidia to yeast at 37°C is essential for virulence. The discovery of a hybrid histidine kinase encoded by DRK1 in Blastomyces and Histoplasma provided the first genetic proof that the morphologic switch to yeast is directly linked to virulence [62]. DRK1 null (DRK1Δ), insertional mutants, and RNA interference (RNAi)-silenced strains grow as hyphae at 37°C instead of yeast, fail to upregulate yeast-phase specific virulence factors such as BADI and CBP1, and are avirulent in a murine model of infection [62]. The function of DRK1 is conserved among the thermally dimorphic fungi. In T. marneffei, DRKA (a DRK1 homolog) is critical for the conversion of conidia to yeast in macrophages [63]. In Sporothrix, Paracoccidioides, and T. marneffei, the transcript abundance of DRK1 is higher in yeast (37°C) than in hyphae (25°C) [63–65]. DRK1 is predicted to function as part of the high-osmolarity glycerol (HOG) signaling cascade, which facilitates adaptation to osmotic, oxidative, and temperature stresses [17]. Accordingly, DRK1 transcription is also upregulated in response to osmotic stress in Paracoccidioides and T. marneffei [63, 65]. In addition to facilitating adaptation to temperature and osmotic stress, DRK1 also influences the integrity of the cell wall [62, 63].

Regulation of the morphologic shift is complex and not limited to DRK1. The transcription factors encoded by RYP1-4 (required for yeast phase) also govern the phase transition and regulate a set of yeast-phase specific genes involved in virulence at 37°C. These transcription factors are upregulated at 37°C and are conserved among dimorphic and filamentous fungi [66–68]. RYP1 is a homolog of the
master regulator WOR1 in C. albicans, whereas RYP2 and RYP3 are part of the velvet complex, VosA and VelB, respectively. RYP4 is a Zn(II),Cys6 zinc binuclear cluster domain protein that is homologous to A. nidulans FacB; however, it does not appear to be involved acetate utilization [68]. These transcription factors form an integrated network in which they directly bind and regulate a common set of core genes including those important for virulence such as CBP1 and YPS3 [68]. Silencing RYP1-4 transcription results in cells that fail to properly undergo the phase transition and grow as hyphae at 37°C [66–68].

The morphologic switch in the opposite direction, yeast to hyphae, is also important for pathogenesis. Growth as hyphae promotes survival in the environment, generation of conidia to facilitate transmission to new hosts, and genetic diversity through mating [1]. B. dermatitidis SREB and H. capsulatum SRE1 encode a GATA transcription factor that governs the transition to hyphae following a drop in temperature from 37°C to 22–25°C [69–71]. SREB null mutants (SREBA) and SRE1-RNAi strains fail to complete the conversion to hyphae [69–71]. The role of this GATA transcription factor on temperature adaptation is conserved in other fungi. A homolog of SREB and SRE1 in C. neoformans, CIR1, is essential for thermotolerance at 37°C [72]. In B. dermatitidis, the defect in the morphologic switch corresponds to a decrease in the biosynthesis of neutral lipids (ergosterol, triacylglycerol) and lipid droplets [70]. Supplementation with exogenous saturated fatty acids (palmitic acid, 16:0, and stearic acid, 18:0) partially corrected the defects in morphogenesis and lipid droplet formation [70]. This suggests that neutral lipid metabolism has to potentially influence the phase transition to hyphae at ambient temperature. SREB and SRE1 also act as negative regulators of genes involved with siderophore biosynthesis and iron uptake; however, this role appears to be independent of the phase transition [69, 70]. In H. capsulatum, deletion of VMA1, which encodes a vacuolar ATPase involved with intracellular iron homeostasis, results in cells that fail to convert to hyphae at 25°C. This indicates the potential for iron metabolism not regulated by SREB to affect the temperature-dependent morphologic switch [73]. In T. marneffei, conversion to hyphae and maintenance of filamentous morphology at 25°C is governed by transcription factors encoded by HGRA and TUPA, respectively [74, 75]. In addition to transcriptional regulators, N-acetylgalcosamine (GlcNAc) accelerates the conversion from yeast to hyphae in B. dermatitidis and H. capsulatum via NGT1 and NGT2 transmembrane transporters [76].

5. In Vivo Transcriptional Profiling

The use of forward genetic strategies such as insertional mutagenesis has substantially advanced the field of medical mycology as related to the thermally dimorphic fungi. This has led to the discovery of novel genes and gene networks that regulate the phase transition (e.g., DRK1, RYP1-3, and SREB). In the age of genome-wide association studies, an untapped reservoir for uncovering novel genes or gene networks in the dimorphic fungi is transcriptional profiling of yeast during infection. To identify genes important for pathogenicity, in vivo transcription profiling was performed for Blastomyces dermatitidis strain 26199 using a murine model of pulmonary infection [77, 78]. A novel, 2-step technique was developed to efficiently separate B. dermatitidis yeast from murine lung tissue to obtain high-quality RNA for RNA-sequencing (RNA-Seq) [77]. To identify B. dermatitidis genes with altered transcription independent of temperature or other conditions, the transcriptional profile of yeast isolated from mouse lungs was compared to yeast cocultured with macrophages at 37°C, yeast grown in vitro without bone marrow-derived macrophages at 37°C, and hyphae at 22°C using K-means cluster analysis [78]. This analysis identified 72 genes that were upregulated in vivo >2-fold and independent of temperature, macrophage cocultivation, and media conditions. A subset of these genes included those that encode proteins secreted into the extracellular milieu, metal cation uptake and transport, and amino acid metabolism [78].

Genes involved with zinc acquisition are upregulated by B. dermatitidis yeast during pulmonary infection. This includes a zincophore (PRA1/ZPS1), high-affinity zinc transporter (ZRT1), and low-affinity zinc transporter (ZRT2) [78]. In Candida albicans, PRA1 is secreted in the extracellular environment to bind zinc and deliver it to the fungus via its interaction with ZRT1 at the cell surface [79]. In C. albicans, Aspergillus fumigatus, and Ustilago maydis, PRA1 and ZRT are coregulated and syntenic. Although PRA1 and ZRT1 appear to be coregulated in Blastomyces, these genes are not syntenic. Surprisingly, PRA1 is not well conserved among the dimorphic fungi and is absent in the genomes of H. capsulatum, Paracoccidioides spp., and Emmonsia; however, homologs are present in Coccidioides. In C. albicans, PRA1 is postulated to impact pathogenesis. Deletion of PRA1 results in mutants that have reduced ability to lyse endothelial cells under zinc-deplete conditions [79]. The impact of PRA1 during in vivo infection has not yet been investigated.

In addition to upregulating zinc-scavenging mechanisms in vivo, B. dermatitidis increases the transcription of NIC1, which encodes a nickel transporter [78]. Nickel is required for the proper function of urease, an enzyme that catalyzes the conversion of urea to ammonia and CO₂. Urea is found in mammalian tissues as a product of purine nucleotide catabolism [80]. In Coccidioides, urease is released from spherules during replication and damages tissue through production of ammonia, which alkalizes the microenvironment [81]. Deletion of the urease gene (UREA) in C. posadasii results in attenuated virulence in murine model of pulmonary infection. At sites of pulmonary infection, UREA cells are unable to catabolize urea in lung tissue and fail to lower the pH (tissue pH7.2 for UREA versus pH7.7 for wild type). Moreover, mice infected with the null mutant exhibited a more organized immune response with well-formed granulomas encasing UREA cells [81]. In Cryptococcus neoformans, NIC1 and URE1 contribute to invasion of the brain. Deletion of either gene results in decreased ability for NICΔ and UREΔ yeast cells to penetrate the central nervous system [82]. URE1 also contributes to the pathogenesis of Cryptococcus gattii, which primarily causes pulmonary infection.
without an increased predilection for CNS invasion in animal models [83, 84]. C. gattii ure1Δ have attenuated virulence during pulmonary infection, reduced capacity to disseminate to the bloodstream, and impaired intracellular replication within macrophages [83].

During pulmonary infection, B. dermatitidis upregulates dioxygenases involved in the catabolism of amino acids [78]. This includes 4-hydroxyphenylpyruvate dioxygenase (4-HPPD, HpdA), homogentisate 1,2-dioxygenase (HmgA), indoleamine 2,3-dioxygenase (IDO), and cysteine dioxygenase (CDG). HpdA and HmgA are conserved among the dimorphic fungi and are localized on a gene cluster [85]. Although the precise role for HpdA and HmgA is not known in B. dermatitidis, research on T. marneffei has illuminated how these genes involved with tyrosine catabolism influence pathogenesis. HpdA and HmgA null mutants are hypersensitive to oxidative stress and have impaired spore germination to yeast in murine and human macrophages [85]. Inhibition of 4-HPPD activity appears to be important for the temperature-dependent morphologic shift. Chemical inhibition of 4-HPPD by NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-cyclohexane-1, 3-dione) in T. marneffei and P. brasiliensis blocks the conversion of conidia or hyphae to yeast following an increase in temperature from 25°C to 37°C [85, 86].

The role of fungal IDO on tryptophan degradation is poorly understood; however, tumor cells upregulate IDO to degrade tryptophan in the microenvironment to evade host immune cells [87]. Pulmonary infection with H. capsulatum and P. brasiliensis induces host IDO, which reduces fungal growth, inhibits Th17 T lymphocyte differentiation, and limits excessive tissue inflammation [88, 89].

In addition to cysteine dioxygenase (CDG), B. dermatitidis upregulates cysteine synthase A (CSA) and a sulfite efflux pump (SSU1) during pulmonary infection [78]. CSA encodes an enzyme involved with the biosynthesis of L-cysteine from acetyl-L-serine. CDG breaks down L-cysteine to L-cysteine sulfonic acid which can be further catalyzed to pyruvate and sulfite. The accumulation sulfite is potentially toxic to cells and is secreted via an efflux pump encoded by SSU1. In C. albicans, deletion of CDG1 and SSU1 impairs hyphal development in the presence of cysteine and CDG1Δ, but not SSU1Δ, and attenuates virulence during murine infection [90]. In dermatophytes such as Arthroderma benhamiae, the catabolism of cysteine to sulfite by CDO1 followed by efflux of sulfite into the extracellular environment by SSU1 is postulated to promote breakdown of keratin to facilitate fungal growth [91]. A. benhamiae CDO1 and SSU1 null mutants have impaired ability to grow on keratin-rich substrates such as hair and nails [91]. On the basis of these data, there is potential that the breakdown of cysteine and sulfite secretion could promote the growth of Blastomyces yeast in skin, which is abundant in keratin and the most common site for extrapulmonary dissemination.

### 6. Conclusions

The thermally dimorphic fungi are a unique group of ascomycetes that are capable of infecting persons with intact and impaired immune defenses. Their ability to adapt to core body temperature (37°C) and transition to yeast morphology is essential for virulence. The morphologic switch to yeast is associated with the upregulation of specific virulence factors that promote adhesion to host tissues, growth in and lysis of macrophages, blunt proper cytokine responses, and impair cell-mediated immunity. The regulation of the reversible transition between hyphae and yeast requires these fungi to adapt and respond to numerous stimuli including temperature, CO2 tension, and sex hormones. In vivo transcriptional profiling has begun to uncover previously unrecognized genes important for propagation and virulence in the mammalian host.

### Conflicts of Interest

The author declares that he has no conflicts of interest.

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