Dimorphism and Pathogenesis in *Mucor* Species

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Abstract

Many pathogenic fungi are dimorphic, in which they switch the morphology between yeast and filamentous forms. This dimorphism has been observed in the Dikarya. Interestingly, the genus *Mucor* is the only group of fungi among the early diverged fungi outside of the Dikarya that exhibits the yeast–hyphae transition. Their morphogenic switch is controlled by environmental factors such as low oxygen and high carbon dioxide concentrations. Genetically, the genes encoding G-protein coupled receptors (GPCR), a serine/threonine phosphatase calcineurin, and subunits of protein kinase A (PKA) all have been documented in the regulation of the dimorphic transitions in *Mucor*. *Mucor circinelloides* is one of causative agents of the deadly opportunistic fungal infection mucormycosis. Similar to other known dimorphic fungi (e.g. *Candida albicans* and *Coccidioides* species), the morphology directly contributes to the virulence of this fungus. Upon entering a host, it grows as filamentous hyphae and invades the host tissue. This chapter further highlights the recent findings on how genes and the environment play a critical role in dimorphism and the virulence in *Mucor* and discusses how these findings can serve as a platform for new therapeutic interventions.

Keywords

Mucor · Dimorphism · Pathogenesis · Calcineurin · Protein kinase A

4.1 Introduction

There is a dramatic variety of cellular morphologies in fungi that can be observed. Two of the most common are the yeast and hyphal morphologies. The ability to shift between two morphologies is referred to as dimorphism. The yeast morphology is characterized as a single cell with a nucleus that reproduces via budding or fission (Sudbery et al. 2004). Typically, this morphology has a spherical or ellipsoid shape that can span a few micrometers in length (Sudbery et al. 2004). Other morphotypes of yeast cells do exist, such as the syncytium, which consists of a single cytoplasm with multiple nuclei (Knop 2011). The hyphal morphology consists of long segments called filaments. These filaments can be 1–30 μm in diameter and can grow from a few microns to meters in length (Islam et al. 2017). Many fungi can transition between yeast and filamentous forms; the dimorphic transition

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between these two morphologies depends on factors such as pH, temperature, and aerobic/anaerobic environmental conditions (Orlowski 1991; Mitchell 1998; Kirkland and Fierer 2018).

Dimorphism shows convergent evolution across the tree of fungi. Most of these fungi belong to the phyla Ascomycota or Basidiomycota, such as *Candida* spp. and *Cryptococcus* spp. (Fig. 4.1a). Many studies indicate that the yeast morphology is only conserved in the Dikarya (Ascomycota and Basidiomycota) and that fungi in the basal lineages do not undergo the yeast form (Laundon et al. 2020). However, yeast growth is also observed in fungi in the phylum Mucoromycota. Mucoromycota has not been included in a yeast-forming group, which is due to only species found in the genus *Mucor* having the ability to grow as yeast (Fig. 4.1b) (Nagy et al. 2017; Laundon et al. 2020). There are three scenarios with regard to the evolution of the yeast morphology. In the first scenario, yeast may have emerged early in the evolution of the fungal kingdom, followed by a loss of the morphology that may have occurred in most basal lineages and some Dikarya clades (Prostak et al. 2021). In the second scenario, the yeast morphology may have emerged prior to the emergence of Mucoromycota and Dikarya. If so, then a loss of the morphology could have occurred in most of the lineages in Mucoromycota and some lineages in Dikarya. In the final scenario, multiple independent convergent evolutions may have occurred in distinct, unrelated clades.

4.2 Dimorphic Transitions in *Mucor* Species

4.2.1 Environmental Factors

Mucor species have been studied longer than most of the world's fungi. They were first described in 1665 in the publication *Micrographia* by Robert Hooke, who described the morphology of a *Mucor* species that grew on his leather belt (Hooke 1667). As time passed and research on Mucorales delved deeper, it was discovered that fungi in the *Mucor* genus are dimorphic (Orlowski 1991; Lee et al. 2013). Interestingly, the hyphal growth of *Mucor* was thought to result from a transmutation of *Saccharomyces* species (Bartnicki-García 1963). However, Louis Pasteur wrote in his book *Études Sur La Bière* that *Mucor* is a filamentous fungus but grows as a multi-budded yeast in conditions with low O_2 and high CO_2 concentrations (Fig. 4.1b), similar to the conditions in the bottom of wine or beer barrels (Pasteur 1876). Bartnicki-Garcia and his colleagues later rediscovered that the major inducer of *Mucor* yeast growth is CO_2 (Bartnicki-Garcia and Nickerson 1962a, b).

Although *Mucor* species exhibit a dimorphic transition in response to various environments, the primary factors that affect the type of growth are the concentration of O_2 and CO_2 and carbon sources (Orlowski 1991). High O_2 concentrations trigger hyphal growth even when fungi are exposed to high concentrations of CO_2 (Fig. 4.1b). This indicates that respiration and mitochondrial function is involved in the dimorphic transition. In fact, chemicals that inhibit mitochondrial function, such as potassium cyanide and antimycin A, which are known to block electron transport, or oligomycin and phenyl alcohol, which inhibit oxidative phosphorylation, can induce yeast growth even in aerobic conditions (Schulz et al. 1974; Gordon et al. 1972; Friedenthal et al. 1974). In addition, chloramphenicol, which inhibits mitochondrial components, results in yeast growth in *Mucor* (Clark-Walker 1973; Rogers et al. 1974). The lipid metabolism inhibitor cerulenin and the S-adenosylmethionine synthetase inhibitor cycloleucine both inhibit the formation of hyphal growth from yeast in aerobic conditions as well (Aoki and Ito-Kuwa 1982; Garcia et al. 1980). Importantly, the addition of bicarbonate that activates adenylyl cyclase or cAMP to the culture media results in yeast growth of *Mucor* (Linz and Orlowski 1991; Lee et al. 2013), implying that protein kinase A (PKA) plays an important role in yeast growth.

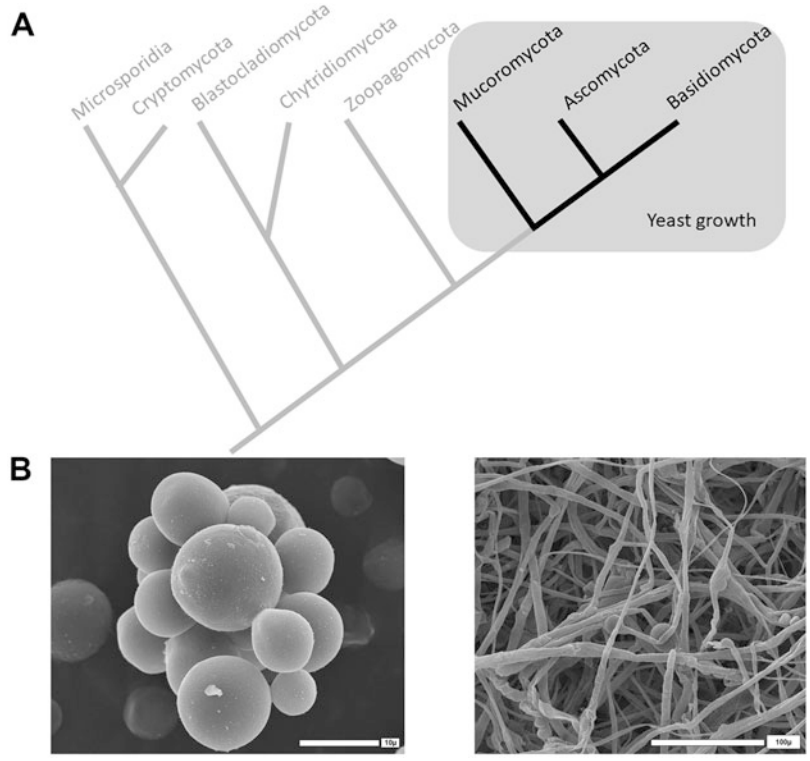

Fig. 4.1 Phylogeny figure. (**a**) Phylogenetic tree of different phyla of fungi. The yeast morphology is found throughout the Dikarya (Ascomycete and Basidiomycota). Fungi in the basal lineages, except for Mucoromycota, do not grow in the yeast morphology or at least have not been observed. (**b**) Two morphologies of *Mucor*. *Mucor* is a filamentous fungus but grows as a multi-budded yeast in conditions with low O_2 and high CO_2 concentrations (left). High O_2 concentrations trigger hyphal growth (right)

4.2.2 Genetics

Dimorphism in *Mucor* species has been documented to be controlled by environmental and genetic cues (Lee et al. 2015; Nadal et al. 2008; Valle-Maldonado et al. 2020). Genetic changes in fungi, such as mutations, generate various detectable signals; the dimorphic fungi receive these signals and may undergo a morphological shift. Currently, there are several documented signaling pathways in the regulation of the dimorphic transitions in *Mucor* - those related to G-protein coupled receptors (GPCR), calcineurin, and subunits of PKA.

Phylogenetic analysis of heterotrimeric G-proteins in fungal species has gained traction in the past two decades. Heterotrimeric G-proteins are abundant across eukaryotic cells; these proteins are fundamental in biological processes, including but not limited to growth, cell differentiation, pathogenesis, and signaling transduction (Li et al. 2007). The heterotrimeric G-proteins are composed of three subunits: Gα, Gβ, and Gγ. Most fungal genomes consist of three Gα, one Gβ, and one Gγ subunits that are conserved (Li et al. 2007). These subunits are attached to the GPCR and sense various ligands (Beckerman 2005; Li et al. 2007). The signaling cascade of the G-proteins is initiated when guanosine triphosphate (GTP) binds to the Gα subunit. The heterotrimeric G-protein dissociates into two signaling components: the Gα–GTP complex and the Gβ–Gγ dimer. Both of these signaling components may regulate downstream effectors. The hydrolysis of the GTP by the Gα subunit results in the reassociation of the heterotrimeric complex (Li et al. 2007).

It has been documented that *Mucor* possesses twelve Gα (Gpa 1–12), three Gβ (Gpb 1–3), and three Gγ subunits (Gpg 1–3), which is the largest collection of heterotrimeric G-proteins in a fungal species (Valle-Maldonado et al. 2015). Phylogenetic and mRNA quantitation analysis of these genes during dimorphic shifting showed that the expression of *gpb1* specifically was upregulated during mycelial growth when compared to spore

or yeast growth, which may indicate that it plays a role in regulating mycelial growth. *gpb3* and *gpg2* are expressed during mycelial growth; in contrast, *gpa1*, *gpb2*, and *gpg2* are expressed during yeast growth (Valle-Maldonado et al. 2015). These results could together outline the biological importance of these genes and the dimorphism in *Mucor*.

Another pathway is the calcium-signaling pathway. Calcineurin is a Ca^{2+}/calmodulin-dependent, serine/threonine-specific protein phosphatase and is a conserved virulence factor in many pathogenic fungi (Vellanki et al. 2020). *Mucor* encodes for one regulatory B subunit (CnbR) and three calcineurin catalytic A subunits (CnaA, CnaB, and CnaC) (Lee et al. 2013). Some nonsynonymous mutations that occur in the genes *cnaA* or *cnbR* result in hyphal growth in the presence of calcineurin inhibitors such as FK506 (tacrolimus) or cyclosporine A (CsA), which indicates that the mutations confer resistance to the drugs. Also, loss-of-function mutations that occurred in the *cnbR* gene, which is necessary for calcineurin activity, result in yeast-locked cells (Lee et al. 2013; Garcia et al. 2017) (Fig. 4.2b). In addition, epimutations in the gene encoding FKBP12, the cellular receptor for FK506, also result in hyphal growth in the presence of FK506 (Calo et al. 2014). These combined findings strongly indicate that calcineurin plays a central role in the morphological transition of *Mucor*.

Additionally, it has been found that when *Mucor* is yeast locked, either genetically or environmentally, PKA activity is elevated. This implies that there is a link between calcineurin and PKA (Lee et al. 2013). The cyclic AMP (cAMP)-dependent PKA signaling pathway is conserved and controls many cellular processes in numerous fungi, such as development, growth, and virulence (D'Souza and Heitman 2001; Kronstad et al. 1998; Taylor et al. 1992). The central components of this signaling pathway have been defined for various fungal species (e.g. *Cryptococcus neoformans*, *Ustilago maydis,* and *Candida* spp.), including the model yeast system *Saccharomyces cerevisiae* (Thevelein and De Winde 1999). The *Mucor* genome harbors multiple copies of the genes encoding two subunits of the cAMP-dependent PKA: regulatory PKA (PKAR) and catalytic PKA (PKAC). cAMP serves as a secondary messenger that regulates PKA activity through the binding and interaction with the regulatory subunit. As a result of this interaction, the catalytic subunit is released, initiating the phosphorylation cascade that causes a dimorphic shift (Taylor et al. 1992). The role of this signaling pathway in regulating morphology and filamentation/branching has been documented using genetic approaches in various fungal species, including *Aspergillus niger* and *Mucor* (Saudohar et al. 2002; Wolff et al. 2002). The regulatory and catalytic subunits are encoded by *pkaR* (regulatory subunit) and *pkaC* (catalytic subunit) genes. Both genes are upregulated under yeast growing conditions. However, only *pkaR* expression is increased when shifting from yeast to filamentous growth. Additionally, the overexpression of *pkaR* results in the multi-branched phenotype. These results together indicate that the PKAR subunit plays a major role in filamentation in *Mucor* (Lübbehüsen et al. 2004; Wolff et al. 2002; Valle-Maldonado et al. 2020).

Notably, one study revealed that calcineurin activity is inversely correlated with PKA activity (Lee et al. 2013). When calcineurin is active, PKA activity is lowered and *Mucor* exhibits hyphal growth (Fig. 4.2a). On the other hand, when calcineurin is inhibited by drugs or the calcineurin gene has loss-of-function mutations PKA activity is elevated, and the fungus is forced to grow in the yeast morphology. Another study found that the *bycA* gene encoding an amino acid permease serves as a link between calcineurin and

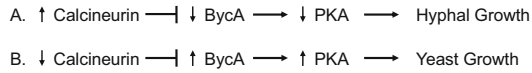

Fig. 4.2 How calcineurin, BycA, and PKA are expressed in the morphogenesis of *Mucor*. (**a**) Calcineurin positively regulates hyphal growth through suppressing *bycA* expression and consequently preventing PKA activity from increasing. (**b**) Under conditions when calcineurin is not functional (either through loss-of-function mutations or drug inhibition), *bycA* gene expression is elevated. BycA then activates PKA, promoting yeast growth in *Mucor*

PKA (Vellanki et al. 2020). Calcineurin negatively regulates the expression of the *bycA* gene, and the *bycA* gene products function as a positive regulator of PKA activity (Fig. 4.2b).

4.3 Dimorphism and Virulence in Pathogenic Fungi

4.3.1 *Candida* Species

In many pathogenic fungal systems, dimorphic transitions play a central role in pathogenesis. The commensal and opportunistic fungus *Candida albicans* has the ability to transition between individual yeast cells and filamentous hyphae (Sudbery et al. 2004) (Fig. 4.3a). As noted above, environmental conditions can initiate the dimorphic transition in different fungi. In *C. albicans*, filamentation can be stimulated when the organism is grown at 37 °C either in serum or in a neutral pH (Mitchell 1998). Dimorphism and filamentation have been known to be a major virulence factor in *C. albicans.* Interestingly, it is known that these filaments adhere well to different surfaces, such as the tubing used in catheters or even mammalian cells. This allows *C. albicans* to form biofilms that can cause chronic infections in immunocompromised patients or patients with medically implanted/indwelling devices (Gulati and Nobile 2016). Another advantage of dimorphism in *C. albicans* can be observed in the evasion of macrophages (Mitchell 1998; Cutler 1991). Some studies have found that yeast cells taken up by macrophages can switch to the hyphal form and lyse the macrophages from within, leading to the successful evasion of the host immune system (Cutler 1991). Additionally, a yeast-locked mutant of *C. albicans* was used to infect mice and was compared to a filamenting strain. In this study, it was observed that the filamentous strain of *C. albicans* was more virulent than the yeast-locked mutant (Cutler 1991).

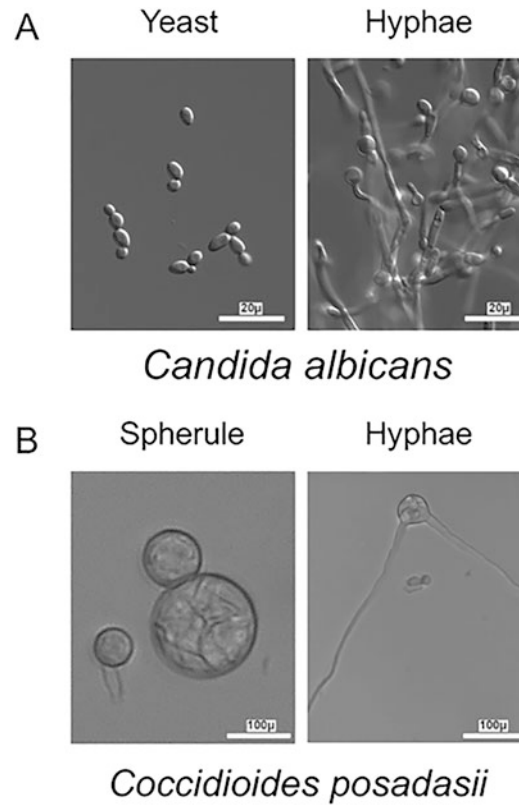

Fig. 4.3 Varying types of morphologies presented by different dimorphic fungi. (**a**) Varying morphologies of *Candida albicans. C. albicans* has three morphologies, with the most two common being the yeast and hyphal form; the third is called pseudohyphae (not depicted), which is an intermittent morphology that exhibits characteristics of both yeast and true hyphae. (**b**) Different morphologies of *Coccidioides* spp. The two major morphologies of *Coccidioides* spp. are the spherules and the hyphae forming long filaments that protrude from the spherules

4.3.2 *Coccidioides* Species

The *Coccidioides* spp. of the dimorphic fungi can also transition between the yeast and hyphal forms. *C. immitis* and *C. posadasii* are the two highly pathogenic fungal species endemic to the arid regions of the western USA (Kirkland and Fierer 2018). These species of *Coccidioides* are known to grow as filamentous mold in the soil

and can form parasitic spherules (Kirkland and Fierer 2018; Parish and Blair 2008). In the wild, the *Coccidioides* spp. form mycelium in the soil (Fig. 4.3b) and make arthroconidia. Once the arthroconidia are released, they can further propagate if the spores land in the soil (Kirkland and Fierer 2018; Cole and Sun 1985). Unfortunately, if the spores are inhaled, the arthroconidia can then form spherules (Fig. 4.3b). These spherules will begin to swell and convert into hundreds of endospores that can then form their own spherules (Cole and Sun 1985). The environmental cues that trigger dimorphism in *Coccidioides* spp. are a temperature change to 37 °C and an increase in CO_2, making animals a perfect host for the replication of spherules (Parish and Blair 2008). Interestingly, it has been found that when the arthroconidia encounter neutrophils they can begin to form spherules as well. This is further backed by evidence showing that in an organ lacking neutrophils, such as the lungs, an attempt to reverse the hyphal form can be observed (Muñoz-Hernández et al. 2014). The dimorphic transition of different fungi can play major roles in their survival in various environments, including an infected host. It is important to understand dimorphism since it can be an excellent target for therapeutic treatments against disease-causing dimorphic fungi.

4.4 Dimorphism and Virulence in *Mucor* Species

Mucor is typically found in the wild as a mold, which poses little threat to healthy individuals. In recent years, *Mucor* has rapidly emerged as a causative agent of the infection mucormycosis (Smith and Lee 2022). Patients who lack a functional immune system are at the highest risk of this infection that has unacceptably high mortality rates of 90–100% in disseminated cases (Reid et al. 2020). When *Mucor* infects an individual, it grows as filamentous hyphae and has been known to invade the host tissue via angiogenesis (Vellanki et al. 2020). The biggest issue related to the mortality of these infections is that Mucorales fungi are intrinsically resistant to most antifungal treatments, making it difficult to contain the infection (Challa 2019). One possible treatment for mucormycosis is to target the dimorphic transition that these fungi make in stressful environments. Studies have found that the yeast-locked phenotype of *Mucor* is avirulent, making dimorphism an excellent target for treating mucormycosis infections (Lee et al. 2013; Lee et al. 2015).

Dimorphism in *Mucor* is governed by calcineurin, and calcineurin inhibitors block the formation of invasive hyphal growth in *Mucor*. Thus, further investigation into *Mucor* dimorphism can provide a platform of understanding the invasive filamentous growth of Mucorales fungi and aid in the development of antimucormycosis drugs. Calcineurin inhibitors such as FK506 and CsA inhibit hyphal growth in *Mucor* and other Mucorales fungi (Juvvadi et al. 2017; Haider et al. 2019; Schwarz et al. 2019; Vellanki et al. 2020). However, these calcineurin inhibitors cannot be used to treat fungal infections in humans because calcineurin is highly conserved in fungi and humans. In humans, calcineurin is required for T-cell function and is a popular target to immunosuppress patients (Williams and Gooch 2012). A recent study suggests that a gene downstream of calcineurin can be targeted to inhibit the calcineurin pathway without the direct inhibition of calcineurin itself (Vellanki et al. 2020). The *bycA* gene is downstream from calcineurin, and its overexpression potentially recapitulates the inhibition of calcineurin seen when calcineurin inhibitors are used. Importantly, this amino acid permease is highly diverged and unique to Mucorales. Therefore, any molecules that directly affect the expression of *bycA* will be excellent calcineurin pathway inhibitors without compromising calcineurin and therefore will have no effect on human calcineurin function.

Among the fungi in the phylum Mucoromycota, *Mucor* species in the Mucorales order are the only ones to exhibit dimorphism between yeast and hyphal growth. This is the only dimorphism observed in the basal fungal

lineages. The yeast phase of fungi is an evolutionary conundrum in which evolutionarily distinct species show both yeast and hyphal growths. In contrast, in other cases of closely related species only one species exhibits dimorphism, but others do not. For example, *C. albicans* is dimorphic and another fungus in the *Candida* clade *Candida lusitaniae* is not (Shapiro and Cowen 2012). The evolution of dimorphism in the *Mucor* lineage is quite interesting. Further comparative genomics followed by genetic manipulations will provide clues to understanding the evolution of dimorphism in *Mucor* and even in the fungal kingdom.

4.5 Conclusion and Future Directions

In the last two decades, many studies have unveiled how genes and the environment play a critical role in the virulence of Mucorales. These studies have shown promising developments in host–*Mucor* interactions and new treatments. Among the recent studies, it was demonstrated that iron uptake systems also play a role in virulence and dimorphism (Navarro-Mendoza et al. 2018), indicating the presence of regulatory factors orchestrating both processes. Therefore, these factors could represent a target for new treatment therapies. Additionally, other studies are currently using antifungal compounds, like FK506, and gene silencing targeting calcineurin to research dimorphism and virulence. Unfortunately, compounds like FK506 do not have a clinical application as an antifungal because of its strong immunosuppressive effect on patients (Hooks 1994). In spite of that, new compounds are needed to target the calcineurin pathway and in tandem with gene silencing could prove to be a promising avenue for new therapies.

It is of interest that only *Mucor* species exhibit yeast-hyphal transition, even when considering other fungi in Mucoromycota and other basal lineages. Has dimorphism only evolved in *Mucor* species? Or is the extent of dimorphism in other basal lineages simply yet to be found? More attention needs to be paid to the basal fungal lineages to address these questions.

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