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Dimorphism in plant and human fungal pathogens

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ABSTRACT

Several plant and human pathogenic fungi exhibit dimorphism by switching between unicellular yeast form to multicellular form under different environmental conditions. The yeast-form cells divide mitotically either by budding or fission to form two independent daughter cells. Plant pathogenic dimorphic fungi include *Ustilago maydis, Ceratocystis ulmi, Taphrina deformans, Mycospharella graminicola, Holleya sinecauda, Verticillium dahliae,* and *V. albo-atrum*. *Ustilago maydis* serves as an excellent model for studying fungal pathogenicity and dimorphism Human infections caused by these fungi are briefly described. The human pathogenic dimorphic fungi comprise several species, viz. *Histoplasma capsulatum, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Sporothrix schenckii, Talaromyces marneffeii* (formerly known as *Penicillium marneffei), Coccidioides immitis/posadosi,* and some species of *Candida*. The phenomenon of dimorphism and the salient feature of infections caused by these fungi are described. A brief mention is made of *Kazachstania bovina*, a dimorphic commensal yeast in the porcine gut, and human infections caused by it. A report of *Candida tropicalis*, a human commensal yeast causing stalk rot of maize in India is also mentioned.

Keywords: Dimorphism, Plant pathogenic, Human pathogenic, Fungi

INTRODUCTION

Many fungi are dimorphic as they can switch between unicellular yeast and a multicellular filamentous form in response to changing environmental conditions. The yeast-form cells divide mitotically either by budding or fission to form two independent daughter cells. During unicellular growth, fungal nuclei divide mitotically, and cytokinesis proceeds either by a budding or a fission process, depending on the species (Alexopoulos *et al.,* 1996; Madhani and Fink, 1998). In growth of filamentous cells, the cells do not separate after nuclear division but rather remain physically joined (Madhani and Fink, 1998). Complete detachment of mother and daughter cells in unicellular form results in the establishment of a self-perpetuating population of single independent cells. In the filamentous stage, the fungal thallus consists of long continuous tubular structures, namely septate filaments (hyphae). Yeast growth is promoted by anaerobic conditions, whereas an atmosphere rich in oxygen stimulates hyphal development. Hyphal compartments form when septae are deposited behind the growing tip of the hypha. These compartments remain connected through pores, and thus maintain a cytoplasmic connection along the hyphae (Alexopoulos *et al.,* 1996; Madhani and Fink, 1998). In some fungi, incomplete wall separation during cytokinesis of budding cells results in the formation of pseudohyphae. Despite the resemblance to a true filament, the septa of a pseudohypha contain no pores, and thus lack a cytoplasmic connection between compartments. This review gives a concise update of our knowledge of dimorphism in fungi, with special reference to fungi infecting plants and humans.

SEARCH CRITERIA

An exhaustive search of existing literature using the Google search engine and PubMed electronic database to identify and download relevant publications on dimorphism in fungi, using several keywords, viz. fungal dimorphism, plant pathogenic fungi, human pathogenic fungi. The Boolean operator 'AND' was used to combine and limit the searches. The publications thus selected were downloaded and relevant information was extracted to incorporate in the review. Cross references were also accessed for information relating to this review.

LITERATURE REVIEW

General aspects

Dimorphic fungi are members of the three major phyla of fungi: *Ascomycota, Basidiomycota* and *Zygomycota*. The largest cluster of thermally dimorphic fungi includes *Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides* and *Paracoccidioides* species of the order *Onygenales*. The order *Ophiostomatales* also includes a number of dimorphic species including the several species of *Sporothrix*. In the large order of *Eurotiales, Talaromyces marneffei* (formerly known as *Penicillium marneffei*) is the only dimorphic species in which yeast cells divide by fission, rather than by budding (Sil and Andrianopolous, 2015). There are very few dimorphic fungi in other phyla, the best-known basidiomycete being *Ustilago maydis* and zygomycete being represented by *Mucor* species (Sil and Andrianopolous, 2015). To understand the essence of fungal *dimorphism, Saccharomyces* species were chosen. In the yeast, *S. cerevisae* the switch from respiratory metabolism to fermentation is the basis for its use in the production of alcohol and in baking. It has also been known that under anaerobic conditions *S. cerevisae* is not able to synthesize sterols and unsaturated fatty acids and these compounds must be added to the media. Yeast growth is favoured by anaerobic conditions, whereas an atmosphere rich in oxygen stimulates hyphal development. A comparison of the cell wall composition of the aerobically and anaerobically growing cells shows major changes in the transcription of more than 500 genes as described in detail by Snoek and Steeensma (2007). Distinct cell walls form between the daughter cells of this yeast after budding (Madhani and Fink, 1998). Filamentous growth is initiated by an asymmetric cell division in which a round yeast cell divides to produce the founding elongated cell of the filament. In another yeast species, *Scizosacchromyces japonicus*, a member of the fission yeast

clade, during the yeast to hypha transmission, the cell evolves from a bipolar to unipolar system with 10-fold accelerated and polarized growth with constant width, vacuoles segregating to the narrowing half of the cells (Kinnaer *et al.,* 2019). These authors demonstrated two unusual features of *S. japonicus*, firstly the cell lacking a vesicle distribution centre at the hyphal tip, but displaying a more rapid cytoskeleton-based transport than the yeast form; secondly the hyphae remaining mononuclear and undergoing highly asymmetrical cell divisions, one daughter cell inheriting the vacuole and the other the growing tip. This event is induced in response to environmental cues that differ dramatically from one organism to another. in *Saccharomyces*, it is starvation for nitrogen, in *Candida*, a commensal and an opportunistic human pathogen, it is serum (along with other factors) and, in *Ustilago*, which infects corn, it is a putative molecular signal from the host plant (Madhani and Fink, 1998).

DIMORPHISM IN PLANT PATHOGENIC FUNGI

Several species of plant pathogenic fungi are dimorphic, viz. *Ustilago maydis*, *Ceratocystis ulmi, Taphrina deformans, Mycospharella graminicola, Holleya sinecauda*, *Verticillium dahliae,* and *V. albo-atrum.* is by Nadal *et. al.* (2008) described in detail the phenomenon of dimorphism in these fungi. The process of dimorphism in three of these species, namely, *U. maydis, T. deformans,* and *H. sinecauda* is discussed briefly.

Ustilago maydis

Ustilago maydis is a basidiomycetous phytopathogenic fungus responsible for corn smut disease. The formation of 'tumour-like' structures called galls on the maize plant is the distinctive symptom of this disease. The hyphae of *U. maydis* branch extensively on the leaf surface and intracellularly before inducing tumour formation. Within the mature tumour, hyphae give rise to round diploid cells with a specialized cell wall; these are called teliospores (Banuett and Herkowitz, 1996). *Ustilago maydis* switches from a saprobic yeast stage to a pathogenic filamentous form in response to nuclear condition and plant signals. Stable filamentous development takes place only within the maize plant, and it requires the mating of two compatible haploid cells (Madhani and Fink, 1998). Because the resultant dikaryotic filaments can proliferate exclusively in plants, a signal(s) emanating from the living maize plant is hypothesized to be essential for triggering this behavior is a dimorphic fungus with a saprobic, haploid, unicellular phase (the sporidial stage) outside the plant and a parasitic dikaryotic filamentous stage within the plant (Madhani and Fink, 1998). Due to the extensive repertoire of available genetic tools and the easy cultivation of its haploid phase in the laboratory, *U. maydis* serves as an excellent model for studying fungal pathogenicity and dimorphism. In the saprophytic phase, the haploid sporidia divide by budding and are incapable of infecting maize. Only when the mating of compatible sporidia occurs is the fungus capable of parasitic growth. The mating-type a locus consists of two tightly linked genes: mfa1 encoding a lipopeptide pheromone and pra1 encoding a seven-transmembrane receptor (Spellig *et al.,* 1994). This pheromonereceptor system accounts for cell recognition and fusion (Banuett and Herskowitz, 1996). Pheromone binding to its receptor mediates cell recognition and initiates sexual development. At this point, cells arrest in the G2 phase of the cell cycle and prepare to form conjugation tubes (Vollmeister *et al.,* 2012). When conjugation tubes fuse, plasmogamy occurs, but karyogamy is delayed until a later developmental stage, leading to the establishment of a dikaryotic filament. Maintenance of a stable dikaryon requires heterozygosity at the b mating-type locus (Vollmeister *et al.,* 2012).

It may be worth mentioning here of a few reports of human infection caused by *U. maydis*. The first one was from Hungary of skin lesions (Preininger and Durch, 1937-1938) in a 31-years old corn farmer, the second from USA in a 55 years old corn farmer with leptomeningitis (inflammation of the meninges-the tissues that surround the brain or spinal cord) and ependymitis, meaning infection of central ventricular system (Moore *et al.,* 1946); the third case was from India of a brain tumour (collection, or mass, of abnormal cells in the brain) in a 13-years-old girl (Randhawa *et al.,* 1959). This was the first culturally proven case of a plant pathogenic fungus causing human infection.

Taphrina deformans

Taphrina deformans, the causal agent of peach and almond leaf curl, is an archiascomycete, and the best-known representative of a large genus of dimorphic species (Rodrigues and Fonseca, 2003) The yeast phase of *Taphrina* spp. may be cultured with some difficulty, but the filamentous phase cannot be culture on a mycological medium and thus is considered to be obligately parasitic. A rather unusual feature of the life cycle of *T. deformans* involves the budding of ascospores while still within the ascus. This process generates sacs stuffed, full of small yeast cells (Rodrigues and Fonseca, 2003). Inoculation of host leaves triggers the budding to filamentous growth transition in this fungus, which is homothallic as indicated by its capacity to generate asci and ascospores after inoculation with a single budding cell. This is unlike some other *Taphrina* species that are heterothallic (Nadal *et al.,* 2008). Once on the peach leaf, a mitotic nuclear division establishes a binucleate condition. This provides an interesting genetic question as to whether the dikaryon in *T. deformans*, albeit completely homozygous, triggers pathogenic development as seen in *U. maydis*, which, in contrast, requires heterozygosity of the paired nuclei for pathogenic development. The sparse filamentous form ramifies in the sub-cuticle and/or inside the plant cells. Subcuticular asci burst through the cuticle to release their spores. Little is known regarding the triggers of dimorphism

in *Taphrina*, but it is likely a result of host signals and/or ploidy considerations.

Holleya sinecauda

Holleya sinecauda, another dimorphic ascomycete is a pathogen of mustard seeds. In early stage of invasion of plant tissues, it occurs almost exclusively in the yeast form. The yeast form is also prevalent form in the early growth on a solid culture medium; however, however when grown for more than six days, a network of true hyphae is formed (Holley *et al.,* 1984). In liquid media, though short branched pseudohyphae are observed, formation of true mycelium is not prominent indicating that surface adhesion is required to induce dimorphic switch (Holley *et al.,* 1984). Prilinger *et al.* (1997) suggested that a study of molecular basis of budding and filamentous growth in *H. sinecaudia* and comparison with *Ashbya gossypii*, a strictly filamentous fungus would help to elucidate the determining factors of two modes of growth. An advance in this direction helped in the development of dimorphic transformation system based on sequences from *A. gossypii* (Schade *et al.,* 2003)

DIMORPHISM IN HUMAN PATHOGENIC FUNGI

The human pathogenic dimorphic fungi include *Histoplasma capsulatum, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Sporothrix schenckii, Talaromyces marneffeii* (formerly known as *Penicillium marneffei*) and *Coccidioides immitis/posadosi*. Dimorphism in these fungi is intimately associated with their ability to colonize, invade, and survive in mammalian hosts (and is closely linked to stimulation of specific gene products) (Marseca and Kobayahsi, 2000). The phenomenon of dimorphism in these fungi is briefly described below.

H. capsulatum, B. dermatitidis, S. schecnkii* and *P. brasiliensis

H. capsulatum is the etiological agent of *histoplasmosis*, *B. dermatitidis* causes blastomycosis, *P, brasilienis* is the agent of paracoccidiodomycosis and *T. marneffei* causes talarao-mycosis. These dimorphic fungi are phylogenetically related *Ascomycetes* than can exist in saprobic mycelial form in soil, organic debris, dried avian/bat excreta. After spores are inhaled from soil or other environmental sources. they switch from non-pathogenic moulds in soil at room temperature to pathogenic yeast or other form in a mammalian host at 37^{O}C. *Histoplasma capsulatum* occurs in soil, enriched with dried avian/bat excreta. Though *B. dermatitidis* has been isolated from soil several times (mostly from near dog habitats), its definite occurrence in soil has not been yet definitely established. However, it is presumed that it naturally occurs in soil in moist organically rich soils typically near waterways. Burgess *et al.* (2006) detected *B. dermatitidis* in three soil samples from a dog kerrnel near Lexington, Kentucky in USA. It is known that 35 out of 100 of the animals had contracted blastomycosis in the previous year. *S. shenckii* occurs in sphagnum moss, plant detritus, woody materials. In tissue these fungi occur as yeast cells (blastospores) with some differences in their shape and manner of budding. Both *H. capsualtum* and *B. dermatitidis* form oval or sub-globose singly budding cells, but in *B. dermatitidis* the yeast cells are larger, broad-based .and thick walled. In *S. schenckii*, the yest cells are elongated. *P. brasiliensis* forms multiple budding cells in the infected tissue. Dimorphism in *H. capsulatum* and *B. dermatitidis* is intimately associated with their ability to colonize, invade and survive in mammalian hosts and is critically lined to induction of specific gene products (Maresca and Kobayashi, 2000). The mechanisms regulating the witch from mycelial form to yeast form are not fully understood (Sil and Andrianopolous, 2015). It is known that a hybrid histidine kinase senses host signal and triggers the transition from mould to yeast from. The kinase also regulates cell-wall integrity, sporulation, and expression of virulence (Maresca and Kobayashi, 1989; Nemecek *et al.,* 2006). In cultures of *Histoplasma capuslatum*, the transition from one phase to the other can be triggered reversibly by shifting the temperature of incubation between 25^{O}C (mycelial form) and 37^{O}C (yeast form). Mycelia are found in soil and never in infected tissue, in contrast to the yeast form (phase), which is the only form present in patients. The temperature-induced form transition and the events in establishment of the disease state are very likely to be intimately related. Furthermore, the temperature-induced form transition implies that each growth form (phase) is an adaptation to two critically different environments. A fundamental question concerning dimorphism is the nature of the signal(s) that responds to temperature shifts.

Histoplasma and *Paracoccidioides* species cause respiratory and systemic disease in mammals (histoplasmosis and paracoccidioidomycosis, respectively). Disease results from inhalation of aerosolized fungal conidia of the fungus from an environmental source. Severity of disease ranges from subclinical to acute and is largely a function of the dose inhaled and the immunological defences of the host (Salezar *et al.,* 2018).

Dimorphism in *Talaromyces marneffei*

T. marneffei is the only dimorphic species in the large order of Eurotiales and is also the only dimorphic species in which the yeast cells divide by fission rather than budding (Sil and Andrianopolous, 2015). Like other dimorphic fungi, *T. marneffei* produces two distinct forms, unicellular yeasts and multicellular hyphae; the switch between two forms is regulated solely by temperature (Andrianopolous, 2002). So far, both the responding cell component(s) and the mechanism(s) remain unclear. Talaromycosis caused by *T. marneffei* causes progressive infection in humans mostly in HIV-infected subjects in SE Asian countries and northeast India and in the northeastern state of Manipur in India (Vanittanakom *et al.,* 2006). Six additional cases are *T. marneffei* infection have been reported including two each from Manipur and Assam, and one each from Delhi, and

Kerala (describing total nail dystrophy) as reviewed by Gugnani and Sood (2020). Bamboo rats of several species are known to carriers of the fungus in SE Asia include *Rhizomys sinensis* (Chinese bamboo rat), *R. sumatrensis* (Large bamboo rat, Sumatran or Indo-Malayan rat) *R. pruinous* (hoary bamboo rat) and *Cannomys badius* (the lesser bamboo rat) (Vanittanakom *et al.,* 2006). The bamboo rat species found to be carrier of *T. marneffei* in Manipur State in northeast India is *C. badius* (Gugnani *et al.,* 2004). *Talaromyces marneffei* can survive in sterile soil for several weeks but only for a few days in unsterile soil (Joshi *et al.,* 2003). Cao *et al.* (2011) were able to isolate *T. marneffei* from 5 of 43 soil samples collected from the burrows and the surrounding environment of bamboo rats in China. A definite natural reservoir of the *T. marneffei* has yet not been established. It is possible that conidiospores of the fungus from soil or from another source are inhaled and then engulfed into alveolar macrophages via respiratory tract.

Dimorphism in *Coccidioides immitis/posadosi*

The disease caused by *Coccidioides* species. coccidioidomycosis, also known as valley fever because of its wide prevalence in the Central Valley of California (Sil and Andrianopolous, 2015). *Coccidioides* infections are on the rise in endemic areas with > 90% increase in incidence in Arizona and California (USA) between 2001 and 2006 with enormous public health consequences (Hector *et al.,* 2011; Sil and Andrianopolous, 2015). Infection is acquired by inhalation of barrel-shaped arthrocondia of *Coccidioides immiits/posadoi* form soil, its natural reservoir. Following this, the arthroconidia undergo isotropic growth producing spherules (100 µm in size) containing numerous endospores. Rupture of the spherule in host tissues releases these endospores, each of which can develop into a new spherule (Nguyen *et al.,* 2013).

Dimorphism in *Candida* species

Candida species are opportunistic pathogens and are fourth most isolated fungi from nosocomial blood stream infections. A worldwide review of *Candida* infections by Pfaller *et al.* (2011) found *Candida albicans* as the predominant species followed by *C. glabrata*, *C. tropicalis, C. parasitosis,* and *C. krusei*. Blood stream infections due to *C. viswanathi*, another opportunistic pathogen have been reported by Shankarnarayan *et. al.* (2018), The pathogenic species of *Candida* are dimorphic; however, both yeast form and filamentous form occur in the infected tissue and can also be induced in some culture media e.g. cornmeal agar. It may be worth mentioning here a report of *C. tropicalis* causing maize stalk rot in India (Lalaramani *et al.,* 1974). Necrotic spots were observed on the stalk. The pathogenicity tests with pure culture of the *C. tropicalis* isolate were positive in maize and white mice, the fungus was thus termed a biopathogen meaning pathogenic for humans and other organisms e.g. plants (Lalaramani *et al.,* 1974). The phenomenon of dimorphism in *C. albicans* has been described in detail by Jacobson *et al.* (2014). *Candida albicans* is a polymorphic fungus that can grow as budding yeast cells (blastospores), ovoid to elongated yeast cells attached to each other (pseudohyphae) and chlamydospores under distinct conditions. The environmental stimuli generate a network of signal pathways which precisely regulate transition between yeast and hyphal growth (Jacobson *et al.,* 2014

Dimorphism in *Kazachstania* (*Axiozyma*) *bovina*

Kazachstania bovina, first described in 1957 from bovine cecum, is a member of the *Kazachstania* (*Arxiozyma*) *telluris* complex, which includes *K. bovina*, described as *Saccharomyces tellustris* in 1957, as *Candida bovina* in 1958, as *Torulopsis bovina* in 1970, and finally as *K. bovina* in 2005 based on multigene phylogenetic analyses (Kauffer *et al.,* 2022). These authors described nine cases of serious fungal infections caused by *Kazachstania* spp. from Strasbourg, France. All the nine isolates were identified as *K. telluris* by matrix-assisted mass spectrometry; three of these were confirmed as *K. bovina* by internal-transcribed spacer sequencing. All the patients with *Kazachstania* infection were immuno-compromised due to underlying diseases, viz. different types of carcinoma, diabetes, and serious bacterial infections (Kaeuffer *et al.,* 2022). Isolation of *K. bovina* has also been reported from nasal passages of pigeons and caecum of cow in Portugal (Kurtzman *et al.,* 2005).

Malassezia arunalokei

This is a new dimorphic lipophilic yeast species from isolated seborrheic dermatitis patients and healthy individuals from India (Honnavar *et al.,* 2016). It was named so in honour of Arunaloke Chakrabarti, a globally recognized medial mycologist in India. Dimorphism in this species is regulated essentially in the same way as in *C. albicans* and other *Malassezia* species (Patel and Markande, 2019).

CONCLUSIONS

This review presents an update of dimorphic plant and human pathogenic fungi. The phenomenon of dimorphism of some selected species of plant pathogenic fungi, viz*., Ustilago maydis, Taphrina deformans*, and *Hollea sinocauda* and plant infections caused by them are adequately discussed. Dimorphism process of converting from mycelial form in a natural source to yeast/spherule/rounded bodies appearing like yeast cells form in the infected tissue at 37^{O}C in human pathogenic fungi, viz. *Histoplasma capsulatum, Blastomyces dermatitiidis, Coccidioides immiitis/posadoi, Paracoccdioides brasiiensis* and *Talaromyces marnefei* and pathogenesis of human infections caused by these species in aptly described. Dimorphism in *Candida* species is also briefly discussed. A mention is also made of *C. tropicalis* (a human commensal yeast) being a biopathogen.

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