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Microbial Pathogens in the Fungal Kingdom

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Abstract

The fungal kingdom is vast, spanning ~1.5 to as many as 5 million species diverse as unicellular yeasts, filamentous fungi, mushrooms, lichens, and both plant and animal pathogens. The fungi are closely aligned with animals in one of the six to eight supergroups of eukaryotes, the opisthokonts. The animal and fungal kingdoms last shared a common ancestor ~1 billion years ago, more recently than other groups of eukaryotes. As a consequence of their close evolutionary history and shared cellular machinery with metazoans, fungi are exceptional models for mammalian biology, but prove more difficult to treat in infected animals. The last common ancestor to the fungal/metazoan lineages is thought to have been unicellular, aquatic, and motile with a posterior flagellum, and certain extant species closely resemble this hypothesized ancestor. Species within the fungal kingdom were traditionally assigned to four phyla, including the basal fungi (Chytridiomycota, Zygomycota) and the more recently derived monophyletic lineage, the dikarya (Ascomycota, Basidiomycota). The fungal tree of life project has revealed that the basal lineages are polyphyletic, and thus there are as many as eight to ten fungal phyla. Fungi that infect vertebrates are found in all of the major lineages, and virulence arose multiple times independently. A sobering recent development involves the species *Batrachochytrium dendrobatidis* from the basal fungal phylum, the Chytridiomycota, which has emerged to cause global amphibian declines and extinctions. Genomics is revolutionizing our view of the fungal kingdom, and genome sequences for zygomycete pathogens (*Rhizopus*, *Mucor*), skin-associated fungi (dermatophytes, *Malassezia*), and the *Candida* pathogenic species clade promise to provide insights into the origins of virulence. Here we survey the diversity of fungal pathogens and illustrate key principles revealed by genomics involving sexual reproduction and sex determination, loss of conserved pathways in derived fungal lineages that are retained in basal fungi, and shared and divergent virulence strategies of successful human pathogens, including dimorphic and trimorphic transitions in form. The overarching conclusion is that fungal pathogens of animals have arisen repeatedly and independently throughout the fungal tree of life, and while they share general properties, there are also unique features to the virulence strategies of each successful microbial pathogen.

Introduction

Infectious diseases remain one of the most significant threats to human health (Cohen, 2000; Jones et al., 2008; Morens et al., 2004). In contrast to chronic diseases such as heart disease and cancer, infectious diseases represent a threat capable of causing extinction and thus have

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the capacity to threaten the very survival of our species. In addition, infectious diseases are subject to rapid evolution and emergence, given the rapidity of their life cycles and large population sizes for disease-causing microbes. Among pathogenic microbes, the eukaryotic pathogens (fungi, parasites) are increasing in incidence, drug resistance is of mounting concern, and there are fewer drugs or vaccines available compared to bacteria and viruses.

The emergence of microbial pathogens involves several routes, including zoonotic transmission from animals to humans, changes in host or vector range, environmental change, and changes to the pathogen via genetic exchange. Genome reassortment of influenza leads to antigenic shifts, necessitating annual changes in vaccine strains and which can lead to pandemics (Lambert and Fauci, 2010). Bacteria predominantly exchange genetic material via horizontal gene transfer (transformation, conjugation, transduction). In both fungi and parasites, genetic exchange is mediated via sexual reproduction (Heitman, 2006, 2010). Sex generates genetic diversity, can promote and transmit drug resistance, and plays roles in pathogenesis and virulence cycles including infectious propagule production.

Our understanding of the origins of fungal microbial pathogens begins with the eukaryotic evolutionary tree of life, which has been redrawn over the past decade based on molecular phylogenetic studies (Baldouf and Palmer, 1993). A key insight was the realization that fungi and animals share a much more recent ancestor than had been appreciated and that the two are sister kingdoms within the opisthokont supergroup lineage of the eukaryotes, which shared a last common ancestor as recently as one billion years ago (Figure 1) (Baldouf and Palmer, 1993; Wainright et al., 1993). The last common ancestor from which all animals and fungi descend is thought to have been unicellular, aquatic, and motile, with a flagellum. There are extant species that closely resemble this hypothesized last common ancestor, and one is the unicellular choanoflagellate *Monosiga brevicolis*. Its genome is ~40 MB and encodes ~9,000 genes, which is about the size of a fungal genome but instead this organism is more closely related to the animal kingdom and serves as a pre-metazoan model for the evolution of metazoans (King et al., 2008). There are also extant fungi that look quite similar, and they are called the chytridiomycetes and are also aquatic with flagella. It is hypothesized that the flagellum was lost once in the fungal kingdom, as fungi exited the oceans and evolved to grow on land as mycorrhiza with the first land plants (Heckman et al., 2001; Liu et al., 2006; Simon et al., 1993). The ongoing UNICORN genome project seeks to understand how unicellular organisms evolved to be multicellular in both the animal and fungal kingdoms, and ten species are being targeted for sequencing (Ruiz-Trillo et al., 2007; Sebe-Pedros et al., 2010a; Sebe-Pedros et al., 2010b). Considering who the fungi are, how they evolved, and their relationships to the animal kingdom will be of general and broad significance.

Traditionally the fungal kingdom has been divided into four phyla: two that share a monophyletic origin (the dikarya: Ascomycota, Basidiomycota) and two considered to be the basal fungi (Zygomycota, Chytridiomycota). However, the fungal tree of life project (AFTOL) revealed that the basal phyla are both polyphyletic, and thus as many as 8 to 10 phyla populate the fungal kingdom (James et al., 2006; Schüßler et al., 2001; Stajich et al., 2009). Microbial pathogens have evolved independently and repeatedly throughout the fungal phyla, and thus while some common shared virulence pathways have emerged such as that involving the protein phosphatase calcineurin (Blankenship et al., 2003; Chen et al., 2010b; Odom et al., 1997; Steinbach et al., 2007) many pathogens have unique virulence strategies, necessitating studies of each species in its own right.

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Chytridiomycetes: *Batrachochytrium dendrobatidis* and global amphibian decline and extinction

One of the most sobering recent developments is that a fungus from the most obscure fungal phyla, the Chytridiomycota, has emerged and is globally causing devastating amphibian declines and numerous species extinctions (Figure 2) (Fisher et al., 2009). This species, *Batrachochytrium dendrobatidis*, or *Bd* for short, is aquatic with a flagellum. It infects the skin of frogs and other amphibians and perturbs their water balance and is often fatal. There is molecular phylogenetic evidence that this global outbreak is largely clonal (James et al., 2009;Morehouse et al., 2003), whereas studies of some unique populations reveal evidence for a higher level of diversity and the possibility of ongoing sexual reproduction (Morgan et al., 2007). Importantly, Koch's postulates have been satisfied from experimental infection studies establishing that *Bd* causes lethal infection of frogs (Lips et al., 2006;Nichols et al., 2001).

How *Bd* arose and swept the globe is an area of active investigation, but given the highly clonal nature of the outbreak isolates, the most parsimonious model is that the organism has been distributed from an ancestral source through some ubiquitous route rather than arising multiple times independently. A variety of models have been advanced, and one unifying hypothesis is that frogs and amphibians that can be colonized but do not succumb to disease serve as carriers. *Xenopus laevis*, commonly used for lab studies and also earlier for pregnancy testing, has been globally exported from Africa and has been proposed as the source and vector of transmission (Weldon et al., 2004). Further studies exploring other vectors, such as the American bull frog, and other possible ancestral geographic sources such as South America (Tim James and Russell Poulter, pers. comm..) are clearly warranted given the severity and implications of this pandemic. While it has been suggested that global warming may be contributing (Pounds et al., 2006)), other studies dissent from this opinion (Rohr et al., 2008), and it is also the case that higher temperature can promote clearing of the infection (Richards-Zawacki, 2010). Heroic efforts to treat infected animals with itraconazole or other antifungal drugs have thus far been successful in captivity (Forzan et al., 2008; Tamukai et al., 2010), but only partially successful in nature, as re-introduction to the wild frequently results in re-infection, or re-emergence of long term latent infection.

The role of *Bd* in ongoing devastating species collapse and extinction events (Crawford et al., 2010) may provide insights into historical events that profoundly altered the trajectory of the animal kingdom on Earth. Arturo Casadevall proposed a provocative model that fungi were involved in the extinction of the dinosaurs (Casadevall, 2005). We know that ~65 million years ago, a meteor struck the Yucatan Peninsula, and the Earth was enveloped by a resulting dust cloud that killed many of the animals and plants on the planet. As a consequence, a fungal bloom ensued that degraded the ubiquitous dead and decaying plant material. We know this because adjacent to the iridium peak in the fossil record we can see a layer of fungal spores at the KT boundary (Vajda and McLoughlin, 2004). This fungal bloom is thought to have given rise to a high density of aerosolized fungal spores, and conjectured to have infected the dinosaurs that were thought to be either poikilothermic (cold-blooded) or only partially homeothermic, and therefore unable to restrict the growth of fungi afforded by the higher core body temperature present in mammals (Bergman and Casadevall, 2010). As a consequence, the mammals flourished and emerged to become the dominant life form on the planet, replacing the dinosaurs and other reptiles. That *Bd* is causing contemporary extinction events lends support to the notion that infectious diseases caused by fungi may have dramatically shaped the evolutionary trajectory of life on our planet, including that of our own species.

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Zygomycete pathogens--*Rhizopus* and *Mucor*

Our understanding of zygomycete fungi, including *Phycomyces* as a model of environmental sensing and sexual reproduction (Cerda-Olmedo and Lipson, 1987);(Idnurm et al., 2006; Idnurm et al., 2008; Sanz et al., 2009), and *Rhizopus* and *Mucor* as common and devastating pathogens of humans, is undergoing a renaissance with the impact of their completed genome sequences (Ma et al., 2009) (Figure 2). *Rhizopus oryzae*, *Rhizopus delemar*, and *Mucor* sp. cause devastating mucormycosis infections in humans that are difficult to treat because of resistance to many common antifungal drugs, and thus management can require surgical debridement and is in many cases fatal. Studies capitalizing on insights from the genome sequences have begun to explore virulence mechanisms involving iron acquisition or its therapeutic deprivation (Ibrahim et al., 2007; Ibrahim et al., 2010), the roles of mating type in sex determination and possibly in virulence (Gryganskyi et al., 2010; Lee et al., 2008)given precedents with other fungal pathogens such as *Cryptococcus* (Kwon-Chung et al., 1992; Nielsen et al., 2005b; Nielsen et al., 2005; Okagaki et al., 2010), and the roles of the dimorphic transition between hyphae and a multibudded yeast evoked by growth under anaerobic conditions and high CO_2 (Bartnicki-Garcia and Nickerson, 1962; Pasteur, 1876). Finally, an interesting example of size dimorphism has emerged from studies of conidia, with links to virulence (Li et al., 2010a). Clearly much remains to be learned about the molecular and genetic basis of virulence evolution in the *Mucorales* phylum of the Zygomycota, but the future is a bright one with the advances afforded by the genome projects driven by the Broad Institute Fungal Genome Initiative and the DOE Fungal Kingdom genome project working in concert with community coordinators and collaborators.

An interesting recent development has emerged from genomic comparisons of the basal and other fungi with the microsporidia, an unusual group of obligate intracellular eukaryotic microbial pathogens that are closely aligned with the fungi, either as true fungi or as a sister group just outside the gates of the fungal kingdom (Keeling, 2009). More than 1,200 microsporidian species are known, of which 13 infect humans and others are implicated as a causative agent for bee hive collapse (Bromenshenk et al., 2010). They harbor highly reduced genomes, as small as 2.9 MB and <2,000 genes for *Encephalitozoon cuniculi* (Katinka et al Science 2001). Moreover, they have lost multiple pathways that normally serve to generate metabolic energy and ATP including the TCA cycle, fatty acid beta oxidation, ATP synthase, and the respiratory electron transport chain. Instead they acquired via horizontal gene transfer bacterial/chlamydial ATP transporters that enable them to usurp ATP from the host cytoplasm (Tsaousis et al., 2008) and even import ATP into their remnant mitochondria, the mitosome (Williams et al., 2002). Recent whole genome comparisons based on gene synteny provide evidence for their shared ancestry and emergence from within the fungal kingdom, and analysis of gene fusions that are shared in metazoans, choanoflagellates, and filasterea, but not in the fungi or microsporidians, further support their alignment (Lee et al., 2008; Lee et al., 2010). As genomes from other fungal phyla are sampled for the first time, further whole genome comparisons of this evolutionary relationship will become possible to understand how such a unique and highly successful group of obligate eukaryotic intracellular pathogens emerged.

Basidiomycetes--Animal and plant fungal pathogens

Fungal pathogens of both animals and plants have evolved repeatedly and independently in the dikarya, both in the Basidiomycota and the Ascomycota. These two broadly successful phyla have a common shared origin estimated to be ~500 million years ago (Figure 2). Two species, *Cryptococcus neoformans* and *Cryptococcus gattii*, have risen to prominence as common pathogens of humans (Cryptococcus ASM Book, 2011). They are ubiquitous in the

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environment, associated with pigeon guano or trees as an arboreal niche. We have all been exposed by inhalation of desiccated yeast cells or spores, which are small enough to penetrate into the alveoli of the lung and cause an initial pulmonary infection that frequently disseminates to the CNS to cause meningoencephalitis. Recent studies from the US Centers for Disease Control reveal that *Cryptococcus* causes more than one million cases of infection annually, >620,000 attributable deaths, and ~one-third of all AIDS associated deaths, now surpassing tuberculosis as a cause of death in Africa (Park et al., 2009). The majority of these cases are attributable to *C. neoformans* causing infection in the context of the AIDS pandemic.

Also of considerable concern is an outbreak of *C. gattii* that began on Vancouver Island in 1999 in both humans and animals, and which has now expanded into the US in both Washington and Oregon (Bartlett et al., 2010; Datta et al., 2009). In this case, >50% of infected patients were otherwise healthy, and their clinical course can be complicated, resulting in up to 20–33% mortality (Bartlett et al., 2010; DeBess, 2010). We now know from the work of Karen Bartlett (an environmental microbiologist at the University of British Columbia, Vancouver) that the organism is endemic throughout the region, associated with soil and a variety of indigenous tree species, such as Douglas Fir, and that particles small enough to be spores are present in the air. Based on molecular phylogenetic analysis, three clonal isolates are responsible for the outbreak. Two are found on Vancouver Island and now also in the US (VGIIa/major, VGIIb/minor), and one is thus far unique to Oregon (VGIIc/novel) (Byrnes et al., 2009; Byrnes et al., 2010; Fraser et al., 2005a; Kidd et al., 2004). The outbreak isolates are sexually fertile, and population genetic studies provide evidence they are part of a recombining global population (Byrnes et al., 2010; Fraser et al., 2005a; Fraser et al., 2005b). That the outbreak isolates are unisexual and all of the α mating type, combined with the finding of a diploid intermediate and molecular analysis of the mating type locus, provides evidence for models in which an unusual form of sexual reproduction, unisexual or same-sex mating (Figure 3), has contributed to both the origins of hypervirulent clones and the ongoing production of infectious spores (Fraser et al., 2005a; Lin et al., 2005). Moreover, given that the VGIIb/minor lineage on Vancouver Island is indistinguishable from isolates from a fertile, recombining, unisexual population in Australia at 30 MLST loci provides evidence that this outbreak lineage may have originated in Australia (Campbell et al., 2005a; Campbell et al., 2005b; Fraser et al., 2005a), and may have been transported to Vancouver Island with imported eucalypts and then made the jump to indigenous host tree species with which it is now associated.

Another group of basidiomycete species, the *Malassezia*, has emerged as frequently associated with humans and linked to common skin disorders, including atopic dermatitis (eczema) and dandruff. The genomes for two species, *M. restricta* and *M. globosa* have recently been determined and reveal considerable insight (Xu et al., 2007). First, their genomes lack the enzyme fatty acid synthase, providing a neat explanation why these fungi are fastidious and must be cultured on media containing lipids. It also provides an interesting explanation for their ubiquitous association with human skin--it is there that they can scavenge lipids from our sebaceous secretions that they require for growth. As a consequence, they are uniquely specialized to survive on human skin and are readily transferred human to human, which impacts their evolutionary trajectory as highly successful commensals or pathogens of humans. Second, the genome and previous phylogenetic studies revealed a close relationship of the *Malassezia* sp. to *Ustilago maydis*, a highly successful basidiomycete pathogen of maize (Kamper et al., 2006). Remarkably, analysis of the secreted enzyme repertoire of *Malassezia* and *Ustilago* reveals marked differences, which likely occurred as one group evolved to colonize human skin (lipases, proteases) and the other plants (cutinases, glycosyl hydrolases). In fact, the secreted enzymes of *Malassezia* are more similar to those of the distant ascomycete human pathogen

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Candida albicans than they are to the more closely related plant pathogen. Third, and most provocatively, the *Malassezia* genomes reveal the potential for an extant sexual cycle in that a mating type locus and meiotic machinery are present. And while no sexual reproduction has yet been observed for this group of species, the fact that the mating type locus is organized similarly to the fused locus present in the bipolar species *Ustilago hordei*, a plant pathogen that infects barley and rye, suggests that there might be two mating types (Bakkeren et al., 2008; Hsueh and Heitman, 2008). A further speculation is that sex might occur on the skin of the infected human host, which is known to occur with *C. albicans* (Lachke et al., 2003), and this might lead to the production of novel antigens that stimulate immune responses in the skin linked to inflammatory diseases such as eczema. To quote the New Zealand Herald's popular press summary: “they found that not only does an icky fungus live on your head and cause dandruff, but it could be having sex. On your head. Right now.”

Ascomycetes--- Roles of sex, dimorphism, RNAi, and light sensing in virulence

We will close with the most successful, and most populated, phyla of the fungal kingdom, the Ascomycota, in which there are myriad pathogens of both animals and plants (Figure 2). Given the success of this group both as fungi and as microbial pathogens, we could devote an entire lecture or review to just this group. Instead we will consider a brief survey and the general themes that emerge. First, it is clear that microbial pathogens have emerged not only independently in the different phyla of the kingdom, but also multiple times independently even within phyla. In the Ascomycota this spans organisms as diverse as: 1) the archiascomycete *Pneumocystis* sp., which are unculturable, infect the lungs to cause pneumonia, are transmitted animal to animal, and have speciated in concert with their hosts such that there are unique pathogens restricted to humans, or mice, or rats, and so on, 2) the hemiascomycetes including *Candida* sp. that are part of our normal GI and skin microbiota and which cause systemic, mucocutaneous, and cutaneous infection, and 3) the euascomycetes including *Aspergillus* sp., the dimorphic fungal pathogens *Histoplasma capsulatum* and *Coccidioides immitis* and others, and the dermatophytes such as *Trichophyton rubrum*, the causative agent of athlete's foot.

Studies on the fungal pathogens in the Ascomycota are legion, and critical given the ubiquity and frequency with which they cause human disease. Recent highlights from an evolutionary perspective include the *Candida* pathogenic species comparative genome project enabling cross-species studies of biology and virulence strategies (Butler et al., 2009), and the discovery that *C. albicans* has at least an extant parasexual cycle, including both heterothallic mating and the recent discovery of homothallism involving same-sex mating (Figure 3) (Alby et al., 2009; Heitman, 2009). Given the previous discovery of same-sex mating in *Cryptococcus* (Lin et al., 2005; Lin et al., 2010; Lin et al., 2007; Lin et al., 2009), the finding that two of the three most successful human pathogens have both retained sexual cycles including both opposite-sex mating heterothallic out-crossing and homothallic same-sex mating that can promote inbreeding suggests a benefit of both forms of sexual reproduction. This may involve the amount of genetic admixture that occurs, giving rise to diversity vs. clonal population structures that may be uniquely adapted to changing vs. more static niches, such as the host. Same-sex mating arose independently in the two species given the ~500 million year evolutionary divide between them, and thus it seems quite likely that there will be other examples of same-sex mating that remain to be discovered in the fungal kingdom, and possibly among those that infect animals given the precedent set by the first two paradigms (Figure 3).

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Possible virulence roles for mating pathways beyond sex have also begun to emerge. For example, pheromone signaling in *C. albicans* can promote biofilm formation which may, in some cases, serve as a prelude to mating, but in other settings may serve to facilitate formation of adherent, drug-resistant biofilms (Daniels et al., 2006). And recent studies have revealed a remarkable example of size dimorphism in which the basidiomycete *Cryptococcus* forms giant cells as large as 50 microns in the lungs of infected animals. Giant cell formation is enhanced during co-infection with cells of opposite mating type, and genetic analysis provides evidence for a paracrine signaling pathway evoked by mating pheromone acting via the Ste3**a** receptor on **a**-cells, analogous to quorum sensing in bacteria (Okagaki et al., 2010; Zaragoza et al., 2010). Hence, cell signaling circuits may dually govern both mating and virulence, and therefore be subject to distinct evolutionary pressures to serve two functions.

The ongoing dermatophyte genome projects at the Broad Institute and the University of Jena promise to revolutionize our understanding of this ubiquitous group of highly successful species that have a monophyletic origin. Genetic and genomic tools are advancing (White et al., 2008), and the identification of the mating type locus and recapitulation of sexual cycles advances both classic genetic approaches and enables tests of when and where sex might occur to impact the organism (Li et al., 2010b). As just one example, the *T. rubrum* population is known to be highly clonal and unisexual. Studies of *T. rubrum* sexual capacity are underway (Anzawa et al., 2010)and promise to be of considerable interest, possibly as a third example of unisexual same-sex mating either on its own or with assistance from closely aligned species in which both mating types remain extant via cross-species pheromone signals. In fact, just this type of ménage a trios mating in which one partner stimulates fusion of two cells of the same mating type has been well documented in both *Cryptococcus* (Hull et al., 2002; Hull and Heitman, 2002; Lin et al., 2005) and *C. albicans* (Alby et al., 2009). We would be remiss to not herald the recent discovery of an extant sexual cycle for *Aspergillus fumigatus* (O'Gorman et al., 2009), which involves culture on oatmeal agar in the dark for incubation periods as long as six months! With this discovery, the triumvirate of the three most successful systemic human fungal pathogens (*Cryptococcus*, *Candida*, *Aspergillus*) have all been revealed to have extant sexual cycles, and unusual ones involving unisexual, parasexual, or delayed sexual reproduction.

The general theme that has emerged from fungal genomics is that there appear to be few, if any, truly asexual fungi. Instead, each genome has revealed, even for anamorphic fungi with no known sexual cycle, that the machinery for both mating and meiosis, including the mating type locus, are conserved. We are drawn to the conclusion that the vast majority of fungi, perhaps even all, have a sexual nature that in many cases remains to be discovered under laboratory conditions. For the pathogenic fungi, these sexual cycles are often rare or cryptic, leading to clonal populations punctuated by limited recombination, with broad implications for the evolution of eukaryotic microbial pathogens including fungi, parasites, and oomycetes (Heitman, 2006, 2010).

Transitions in form are common throughout the fungal kingdom (Bastidas and Heitman, 2009; Odds, 1988). For example, *Mucor* is dimorphic growing commonly as a multinucleated hyphal form, yet switches to a multi-budded yeast under anaerobic conditions and elevated CO_2 (Bartnicki-Garcia and Nickerson, 1962). *Saccharomyces cerevisiae* undergoes a dimorphic transition from yeast to pseudohyphae in response to nitrogen limitation (Gimeno et al., 1992). Yet other fungi such as *A. fumigatus* grow strictly as a filamentous fungus, a growth mode shared with ~80% of fungal species. These transitions in form are not only fascinating, but intimately linked to virulence. For example, the hyphae of *A. fumigatus* are critical for tissue invasion, and in *C. albicans* the yeast cell is essential for dissemination, whereas the hyphal form allows the organism to battle its way

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out of a macrophage following phagocytosis (Lorenz and Fink, 2002; Rocha et al., 2001; Uppuluri et al., 2010). There is no simple rule, for example that hyphae are pathogenic and yeasts are not. *C. neoformans* infections are caused by the yeast mode, whereas the hyphal mode occurs during sexual reproduction in nature. For *C. albicans*, both the yeast and the hyphae are essential for infection, as mutants locked in either growth mode are avirulent. Thus, dimorphic transitions in both directions can be critical, enabling a yeast to switch to hyphae and invade tissue, and a hyphal biofilm to switch to yeast that are released to seed distant tissues.

There is considerable debate on whether the ancestral fungus was a yeast or a hyphae, but given that the last common ancestor was a unicellular aquatic creature with a flagella, that would seem to favor origin as a yeast rather than a hyphae. If so, that suggests that the evolution of hyphal growth was a highly successful one given that only ~20% of species are known to grow as yeasts, many of which are dimorphic and produce pseudohyphae, hyphae, or both. *C. albicans* is one such trimorphic fungus, able to grow as a yeast, pseudohyphae, or hyphae. Whether pseudohyphae or hyphae were distinct developmental fates or part of a continuum (Figure 4) was unclear until recent studies examining the regulated expression of Ume6 provided evidence that yeast can form filaments that contain both pseudohyphae and hyphae (Carlisle et al., 2009). Low levels of Ume6 evoke yeast growth, intermediate levels produce pseudohyphae, and high levels drive hyphae. Moreover, increasing Ume6 from intermediate to higher levels converted pseudohyphae to hyphae, even producing hyphal/pseudohyphal composite filaments. When Ume6 was repressed in hyphal cells, they first produce pseudohyphae and then yeast. Thus, both hyphal growth modes are reversibly orchestrated by the levels of a single key regulatory factor, and this supports models in which pseudohyphae are a way station between yeast and hyphae and not a distinct fate (Figure 4). Recent studies also provide insight into how hyphae can produce yeast cells (Shen et al., 2008). Kohler and colleagues discovered that the pescadillo protein is required for *C. albicans* hyphae to produce yeast cells, and strains lacking pescadillo are locked in the hyphal growth mode, providing insight into how strictly filamentous fungi may have evolved from ancestral yeasts.

Fungal genomics reveals poignant examples of gene loss and retention linked to virulence, and just two are considered here: RNAi and light sensing. The RNAi pathway is central to the ability of organisms to mount defenses to RNA viruses, and also silence transposons. Remarkably, the RNAi pathway has been lost in *U. maydis*, a highly successful pathogen of maize, but retained in the closely related species *U. hordei* (Laurie et al., 2008). Similarly, the RNAi pathway has been lost in *S. cerevisiae*, but retained in the closely related species *S. castelli* and in the pathogen *C. albicans* (albeit with a novel form of Dicer) (Drinnenberg et al., 2009). Many other human pathogens have retained the RNAi machinery, including *Mucor* and *Cryptococcus*, and novel and key roles in silencing both exogenous and endogenous DNA elements have emerged (de Haro et al., 2009; Janbon et al., 2010; Nicolas et al., 2007; Nicolas et al., 2010; Nicolas et al., 2003; Wang et al., 2010). Similar examples of RNAi loss and retention have recently been discovered in *Leishmania* parasite species (Lye et al., 2010), illustrating the generality of this theme.

Light is one of the most pervasive environmental signals that impinges on life, and the ability to sense light has been central to the evolutionary trajectory of animals (vision), plants (photosynthesis), and also the fungi. A panoply of fungal light sensors have been discovered, including phytochromes (red light), opsins (green light), and the white collar protein complex (Wc1–Wc2) (blue light) (Corrochano, 2007; Corrochano and Garre, 2010; Idnurm et al., 2005; Idnurm et al., 2010; Rodriguez-Romero et al., 2010)). These photoperception systems are tuned to photons of different wavelengths across the visible light spectrum. Why might fungi sense not only photons but also their color? One thought is

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that sensing both red and blue light enables fungi to coordinate their behavior with the circadian rhythm of the earth, sensing red light at dawn, the blue sky of day, and then red at sunset. There is even recent evidence that the proteins for blue and red light sensing form a protein complex, serving as something of a primitive eye for the fungi (Blumenstein et al., 2005; Purschwitz et al., 2008). The white collar complex first came to light from studies on photosensory properties of *Neurospora crassa* (Ballario et al., 1996; Chen et al., 2010a; Linden and Macino, 1997). From studies on *Cryptococcus* (Idnurm and Heitman, 2005) and the zygomycetes *Phycomyces* and *Mucor* (Idnurm et al., 2006; Sanz et al., 2009; Silva et al., 2008; Silva et al., 2006), we now appreciate that the white collar complex is an ancient one, and extant in at least the Ascomycota, Basidiomycota, and Zygomycota phyla. It is quite remarkable that while many fungi have found it of evolutionary benefit to retain light sensing, others have lost it entirely, including *S. cerevisiae* and *C. albicans*, apparently as they became specialized to thrive in niches that are predominantly dark (the GI tract) or in which light sensing is not essential, analogous to the blind cave fish that have evolved repeatedly and independently around the globe. It is further quite striking that the model yeast *S. cerevisiae* has lost both the RNAi pathway and light sensing, and fortuitous then that we have other fungi to study for these critical biological processes. This is a recurrent theme throughout mycology, that it is essential to choose a system in which one can explore the biology of interest and to not be limited to model systems or species in which a process or pathway may have been either entirely lost or in which it may be impractical to study.

Fungal light sensing has recently been linked to virulence. First, the white collar orthologs Bwc1 and Bwc2 were found to contribute to virulence of *C. neoformans* in mice, and mutants lacking either protein are attenuated (Idnurm and Heitman, 2005). Thus, fungi may sense light in the environment, and then the relative darkness that surrounds them when they in a host. Analogously, the Wc1 ortholog was found to contribute to the infection of mice by *Fusarium oxysporum* but not for infection of tomato plants (Ruiz-Roldan et al., 2008). Strikingly, recent studies of bacterial pathogens have similarly highlighted a role for photoperception in virulence (Idnurm and Crosson, 2009; Swartz et al., 2007). Recent comparative studies fueled by genome advances reveal that the while the fungal light sensors have been retained in some pathogenic species (*Cryptococcus, Mucor* and *Rhizopus*, *Magnaporthe oryzae*, *H. capsulatum*), strikingly, they have been lost in many others, including the dimorphic fungi *C. immitis* and *B. dermatitidis*, the dermatophytes *T. rubrum* and *Microsporum gypseum*, *C. albicans* and other *Candida* sp., *Malassezia globosa*, *E. cuniculi*, and *B. dendrobatidis* (in this last case, either lost or never present) (Idnurm et al., 2010). While it is understandable why *C. albicans*, which has adapted to survive in the dark environment of the mammalian GI tract, might have eschewed light sensing, it is quite remarkable that fungi that are well adapted to survive on human skin (dermatophytes, *Malassezia*) have apparently lost the capacity to sense light. This is all the more remarkable given that blue light often serves as a proxy for the concomitant presence of DNA damaging UV light, and *bwc1* and *bwc2* mutants of *C. neoformans* are UV sensitive (Idnurm and Heitman, 2005). One possible theory is that these skin adapted fungi lost visible light/UV sensing as a virulence strategy, and now visible light/UV serve to restrain their growth on skin, both promoting commensalism by keeping them at bay and also causing them to survive better in skin microenvironments that are less sun exposed, such as the interdigital toe webs on our feet where they will be shielded from harmful UV rays.

Clearly, much remains to be learned, both about fungal light sensing in general and with respect to virulence strategies of fungal pathogens, but the future promises to be a bright one.

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Coda on the routes to evolution of human fungal pathogens

It is clear that fungal pathogens of animals evolved repeatedly and independently throughout the fungal kingdom, but three general themes emerge. First, for some organisms, their evolutionary fate was from commensal to pathogen. These examples include the pathogenic *Candida* sp., which are part of the normal human microbiota resident on our skin and mucosal surfaces (oropharynx, GI tract, vagina). These organisms run the gauntlet of exposure to immune cells and have evolved and adapted to survive in this milieu, enabling them to survive to varying extents and cause disease in humans and to be transmitted from human to human. *C. albicans* is readily transmitted from mother to fetus during birth, or mother to infant during nursing, and between sex partners. *C. parapsilosis* is frequently transferred from the hands of health care workers to patients. Second, for a series of other fungal pathogens it is debatable whether they are considered part of the normal microbiota, but they commonly colonize or infect humans and are also transmitted human to human. These include the dermatophytes and *Malassezia* sp. resident on our skin that are transferred person to person or via fomites, and *Pneumocystis* sp. in the lung that are transferred by aerosol and inhalation.

Finally, there are many fungal pathogens that are environmental, and each human encounter is unique without evidence for human to human transmission. This includes *A. fumigatus*, *C. neoformans*, *C. gattii*, and the dimorphic human fungal pathogens, among others. This example is the most perplexing. How is it that these organisms can apparently be so well adapted to a human host, despite the seeming lack of human to human transmission? It is frequently posited that these are “accidental” pathogens (Casadevall and Pirofski, 2007). While that is possible, it also seems unsatisfying given the vast numbers of fungi and the vanishly small number that are pathogenic to animals, unless of course these are the few that have just by chance happened upon a successful virulence strategy. However, there are other considerations. First, Arturo Casadevall and others have championed the idea that human fungal pathogens evolved in an evolutionary crucible of heterologous hosts: amoeba, nematodes, insects, and even plants that formed a staging ground for the evolution of virulence (Steenbergen and Casadevall, 2003; Steenbergen et al., 2003, 2004; Steenbergen et al., 2001). One might consider this the Muhammad Ali model of fungal pathogenesis--most fights involve a sparring partner that prepares one for the rare prize fight for the title. Second, there may be more complex animal-environment-animal cycles, or even cryptic animal-animal cycles, that promote virulence evolution. For example, in nature when infected animals are consumed by predation, or die and their carcass decays or is consumed by scavengers, this may return the pathogen to the environment or lead to transmission to a new host. Other modes of animal behavior may also contribute. For example, *C. gattii* frequently colonizes the nares of both Koala and cats, and in this setting may be more readily transmitted animal to animal than currently appreciated during grooming or other activities (Connolly et al., 1999; Krockenberger et al., 2002). If so, these routes may lead to adaptation for survival on and in animals, and thereby select for virulence attributes. Perhaps this begins to provide an explanation as to why *Cryptococcus* is a well adapted facultative intracellular pathogen that survives in macrophages, and elaborates a complex polysaccharide capsule virulence factor in response to host signals, including high CO_2 (Granger et al., 1985). In the specific case of the dimorphic human fungal pathogen *C. immitis*, it is found sporadically in the desert soil, most commonly in association with a decaying carcass. Analysis of its genome reveals a vast expansion of protease genes, and those encoding other enzymes that would be expected to mediate decay of animal tissues, and a loss of enzymes associated with plant degradation (Sharpton et al., 2009). Thus, *C. immitis* appears to have evolved from a plant associated ancestor to adapt to growth on dead or living animal tissue, and this may have promoted the evolution of virulence strategies that render this an evolved rather than an accidental pathogen. Hence, other environmental fungi

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may have similarly evolved the capacity to infect animals, despite not appearing to be frequently contagious.

In closing, these musings about the evolution of human fungal pathogens throughout the fungal kingdom necessarily restrict our thoughts to just a handful of interesting species, but what this perspective reveals is just how powerful a cross species comparative approach is to provide profound insight. Thus, no matter the origin of your particular fascination with the fungal kingdom (pathogens, symbiosis, genetic models, lichens, mushrooms), our potential as the mycology community is in broadly considering what we have to learn not only from those fungi that are the objects of our detailed studies, but what we have to learn from all of the fungi currently under investigation, the legions that remain to be discovered and characterized, and from each other. The future for mycology, and for mycologists, is indeed a bright one.

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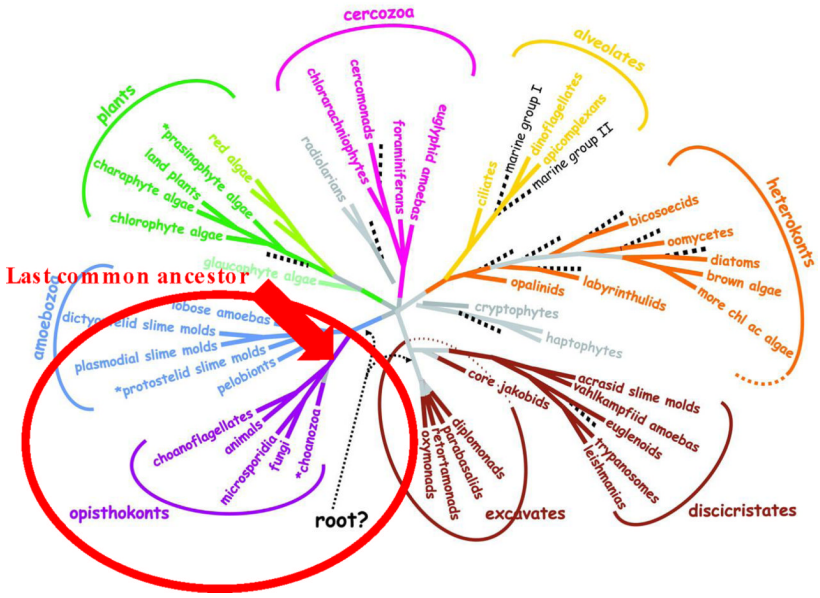

Figure 1. The eukaryotic tree of life

Recent molecular phylogenetic studies revealed the organization of the eukaryotic domains of life stemming from a last common ancestor. In particular, this analysis revealed a unique evolutionary relationship of the fungi and the animals as opisthokonts, sharing a more recent last common ancestor with each other to the exclusion of all other groups of eukaryotes. Modified from Baldauf et al, Science 2003.

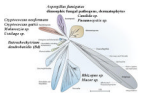

Figure 2. Microbial pathogens in the diverse phyla of the fungal kingdom

Based on the AFTOL project, we now appreciate that the fungal kingdom spans as many as 10 phyla (the microsporidia are not depicted here) (James et al., 2006). Fungal pathogens have evolved repeatedly and independently throughout these phyla, and specific examples discussed in this review are depicted here. Adapted from Figure 1 from Schussler et al, Mycological Research 2001.

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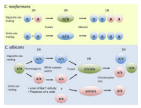

Figure 3. Opposite- and same-sex mating pathways in *C. neoformans* and *C. albicans*

Recent studies reveal that these two common human fungal pathogens have retained extant sexual cycles involving cells of either opposite mating type or the same mating type. In *C. neoformans*, both sexual cycles are complete, including meiotic recombination, and generate infectious haploid spores. C. albicans is an obligate diploid, and mating first requires homozygosis of the MAT locus to produce or α/α or **a**/**a** cells, which undergo white to opaque switching and then fuse to produce a tetraploid zygote that undergoes concerted random chromosome loss to return to the diploid state by a currently recognized parasexual cycle. Same-sex mating can occur in strains lacking the Bar1 protease that destroys α factor, or in the presence of limiting α cells as a pheromone donor. The parasexual cycle of *C. albicans* involves Spo11-dependent recombination, and therefore may also involve cryptic versions of meiosis.

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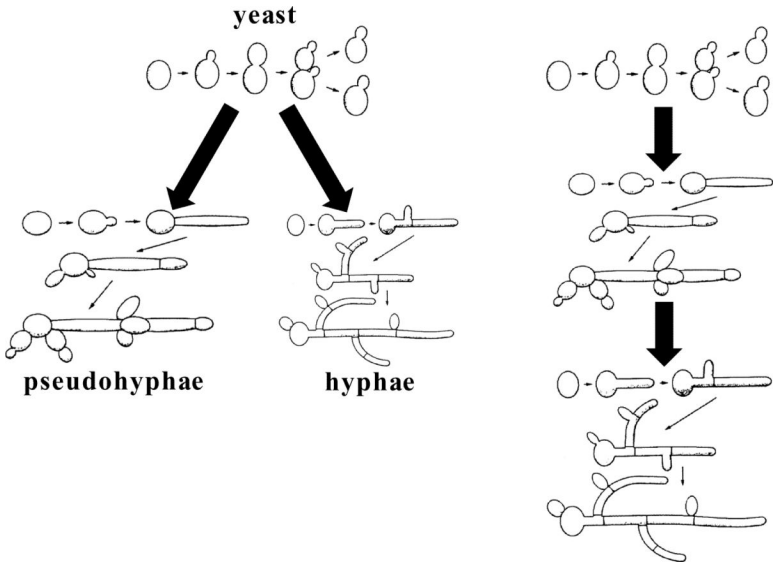

Figure 4. Trimorphic transitions in *C. albicans*

The left panel depicts the transition of *C. albicans* yeast cells to pseudohyphae (left) and hyphae (right) as two distinct developmental fates. The right panel depicts this trimorphic transition as a continuum from yeast to pseudohyphae to hyphae. Recent studies support the continuum model of development. Modified from Figures 5.2, 5.3, and 5.4 from Odds 1988 with permission.