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Pathogenic Fungi Causing Diseases in Humans

Sharwan Kumar Srivastava¹, Mukul Sinha²

Department of Botany, Shri Lal Bahadur Shastri Degree College, Gonda, Uttar Pradesh, India¹

Department of zoology, Shri Lal Bahadur Shastri Degree College, Gonda, Uttar Pradesh, India²

ABSTRACT: Few among the millions of fungal species fulfill four basic conditions necessary to infect humans: high temperature tolerance, ability to invade the human host, lysis and absorption of human tissue, and resistance to the human immune system. In previously healthy individuals, invasive fungal disease is rare because animals' sophisticated immune systems evolved in constant response to fungal challenges. In contrast, fungal diseases occur frequently in immunocompromised patients. Paradoxically, successes of modern medicine have put increasing numbers of patients at risk for invasive fungal infections. Uncontrolled HIV infection additionally makes millions vulnerable to lethal fungal diseases. A concerted scientific and social effort is needed to meet these challenges. Fungal infections today are among the most difficult diseases to manage in humans. Some fungi cause disease in healthy people, but most fungal infections occur in individuals already experiencing serious illness, and frequently jeopardize the success of the newest medical advances in cancer care, solid organ and hematopoietic stem cell transplantation, neonatal medicine, autoimmune disease therapies, trauma and intensive care, and sophisticated surgery. In fact, these medical advances themselves often make their beneficiaries vulnerable to fungal disease. Treatment can involve breaching normal immune functions, or susceptible patients, such as extremely premature newborns who survive long enough to become infected by a fungus.

The following discussion intends to touch on highlights of the evolutionary developments by which living humans became substrates for fungi. Given the tremendous wealth of recent findings on fungal evolution, phylogenetics, genomics, development, and pathogenesis, this overview will necessarily omit much work critical to our understanding of fungi, which the other articles in this collection will focus on in detail. The capability to infect an immunocompetent human has arisen independently multiple times among three major fungal phyla: the Entomophthoromycota, the Ascomycota, and the Basidiomycota.

KEYWORDS: fungi, infects, humans, diseases, pathogenic, illness, medicine, lethal, treatment

I. INTRODUCTION

Entomophthoromycota

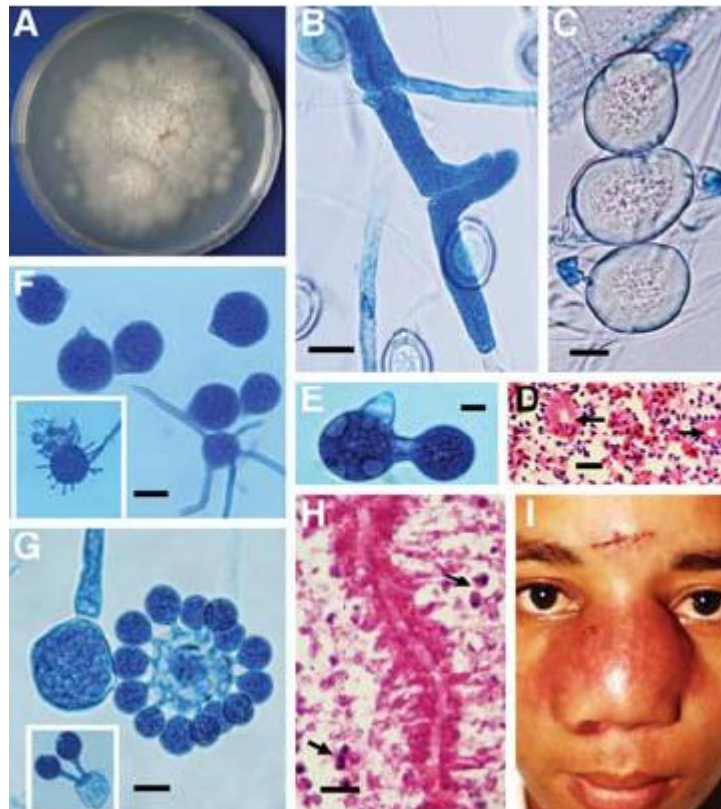
Conidiobolus spp. cause submucosal disease of the nose, sinuses, and central face. In most cases, gradual progression causes swelling of submucosal and subcutaneous tissue, disfigurement, breathing difficulties, and chronic bacterial sinusitis caused by the blockage of ostia. Unlike the Mucorales causing sinus disease, *Conidiobolus* does not usually invade blood vessels nor penetrate into the central nervous system (CNS). *Basidiobolus ranarum* causes subcutaneous disease primarily in children of tropical and subtropical Africa, Asia, and the Americas. Nodules appear at sites of inoculation through insect bites, scratches, or small wounds.[1,2]

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***Basidiobolus ranarum* causes subcutaneous disease primarily in children**

Ascomycota

Pathogenic Onygenales

Several soil-inhabiting members of the ascomycete order Onygenales have evolved to parasitize mammals and cause systemic infection. They have been classified in the family Ajellomycetaceae, which include *B. dermatitidis* (teleomorph, *Ajellomyces dermatitidis*), *H. capsulatum* (teleomorph, *Ajellomyces capsulatus*), *Paracoccidioides brasiliensis*, *Paracoccidioides lutzii*, *Lacazia loboi*, *Coccidioides immitis*, *Coccidioides posadasii*, and related fungi with similar properties. The intracellular pathogenic strategy of some of these organisms is similar in protozoa and macrophages. Disease caused by these fungi begins asymptotically in the lungs and progresses to an influenza-like illness or frank pneumonia. They can disseminate to distant sites, can persist and reactivate, with different organ predilections among different genera: *Paracoccidioides* in oral and respiratory mucous membranes.[3,4]

Their primary lifestyle is saprobic. Most genera occur in defined geographic areas, which follow particular soil consistencies, for instance, dry and alkaline for the *Coccidioides* spp. and acidic for *Histoplasma*. It has not been ruled out that their geographic distribution follows that of specific host mammals. In the soil, they grow as a branched network of hyphal filaments, a mycelium, and saprobically use organic matter. They produce airborne dispersal cells: Conidia produced from specialized hyphae, as *Histoplasma* and *Blastomyces* do, or arthrospores from regulated fragmentation of hyphal compartments, as *Coccidioides* and *Paracoccidioides* do. *Paracoccidioides* produces both

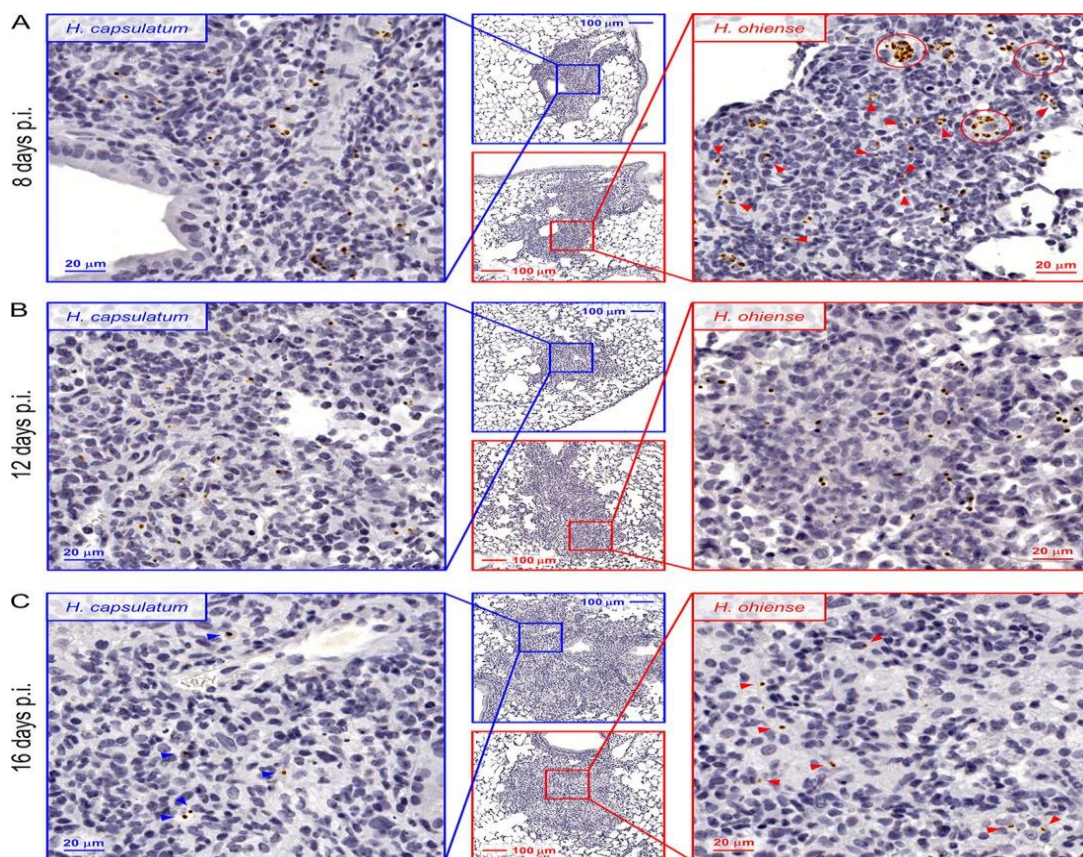
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Vol. 9, Issue 3, March 2020

arthroconidia and aleuriconidia (conidia directly produced along the hyphae). Once conidia or arthrospores are taken up by a mammal, usually by inhalation, they convert into parasitic yeast (or spherules, in the case of *Coccidioides* spp.) and initiate an infection. The principal signal for their conversion to the yeast form is the elevated mammalian body temperature, so that this switch can be induced in vitro when they are cultured at 37°C or above. For this reason they are grouped as thermal dimorphs. These fungi infect, persist, and cause disease in healthy hosts. In immunocompromised hosts, the infections are more clinically apparent, more severe, and more likely to disseminate to multiple organs. Adaptive cellular immunity is required to control the infection with these fungi and can be detected by skin tests with purified antigens. For this reason, clinically apparent infections with some members of this group, such as *H. capsulatum*, became much more common with the rising prevalence of AIDS. These Onygenales (Ajellomycetaceae) are the only phylogenetically related group whose members all cause systemic disease in otherwise healthy people.[5,6]



H. Capsulatum infection

Other thermally dimorphic fungi are *Sporothrix schenckii* (order Ophiostomatales), which is primarily introduced into the host through skin injuries, and *Talaromyces (Penicillium) marneffeii* (order Eurotiales), which does not infect healthy hosts but because of the AIDS epidemic has become a prevalent and important invasive pathogen in Southeast Asia. These fungi coevolved with higher vertebrates, as it is the adaptive immune system by which they are controlled. [7,8]The fact that these evolutionarily distant fungi convert from saprobic hyphal to pathogenic yeast growth at the temperatures of endothermic animals suggests that an ability to access large nitrogen and other nutrient stores of an animal host is an advantageous lifestyle option for a soil dweller, and a result of convergent evolution in several phyla.

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Vol. 9, Issue 3, March 2020

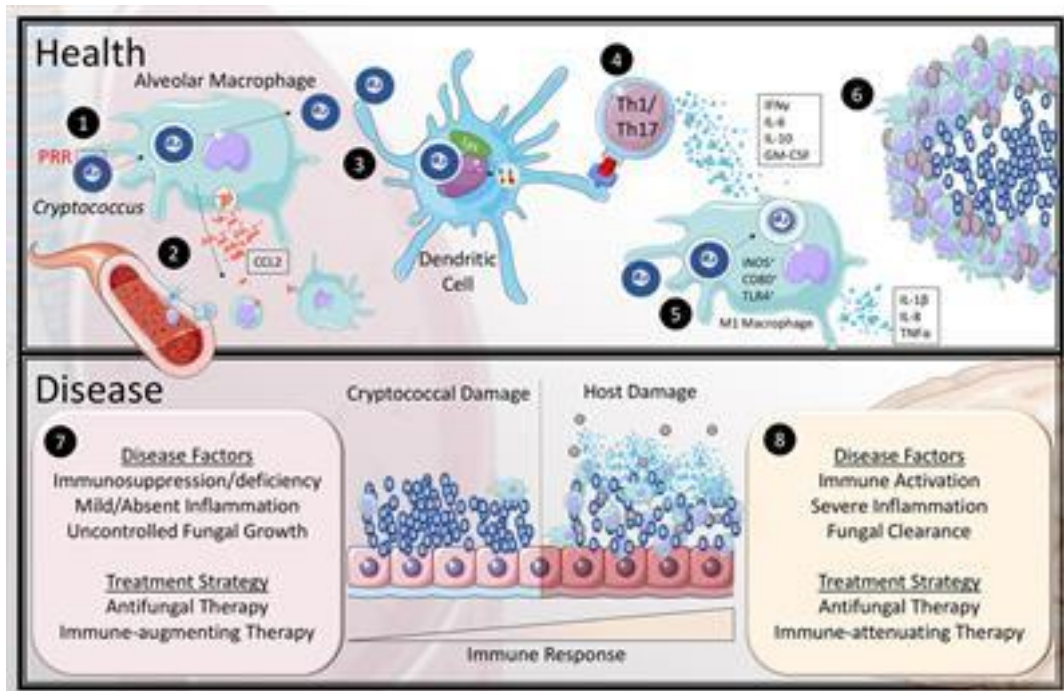
H. capsulatum will be discussed at greater length because it is well studied and also because it exemplifies important principles for other thermally dimorphic Onygenales. This fungus inhabits soil and other organic matter such as decaying wood enriched with bat and bird droppings. Its hyphae produce macro- and microconidia, and the latter are small enough, <5 µm, to penetrate into the alveoli of mammalian lungs. There they are phagocytized by alveolar macrophages and converted to yeast that is able to proliferate in the hostile environment of the phagolysosome.

Aspects of histoplasmosis resemble infections with a well-adapted bacterial intracellular pathogen, *Mycobacterium tuberculosis*. Depending on inoculum size, infection is most often inapparent or leads to a self-limited influenza-like illness. The pathogen can persist indefinitely until immune decline allows it to reactivate. Lung disease resembling TB can ensue immediately after infection, and dissemination to all organs occurs depending on host immune status and age. The response of an immunocompetent host is granuloma formation.[9,10]

II. REVIEW

Basidiomycota

Cryptococci Basidiomycete yeast with a worldwide distribution, cryptococci, in the past century, infected humans only rarely.



Cryptococcal damage

The pathogenic cryptococci, *C. neoformans* and its sister species *C. gattii*, enter a human by inhalation of infectious cells: dried yeast or possibly basidiospores, the products of meiosis after mating. When these small airborne cells, <5 µm in size, are inhaled, pneumonia can ensue in susceptible hosts, and on gaining access to the bloodstream, [11,12] the yeast can disseminate to all organs. *Cryptococcus* has a special predilection for the CNS and causes subacute meningoencephalitis, in which high intracranial pressure plays an especially deleterious role, which, if left untreated, is lethal. The fungus can persist for years in the lung or in sites of previous dissemination and reactivate only on weakened immune surveillance.

International Journal of Innovative Research in Science, Engineering and Technology

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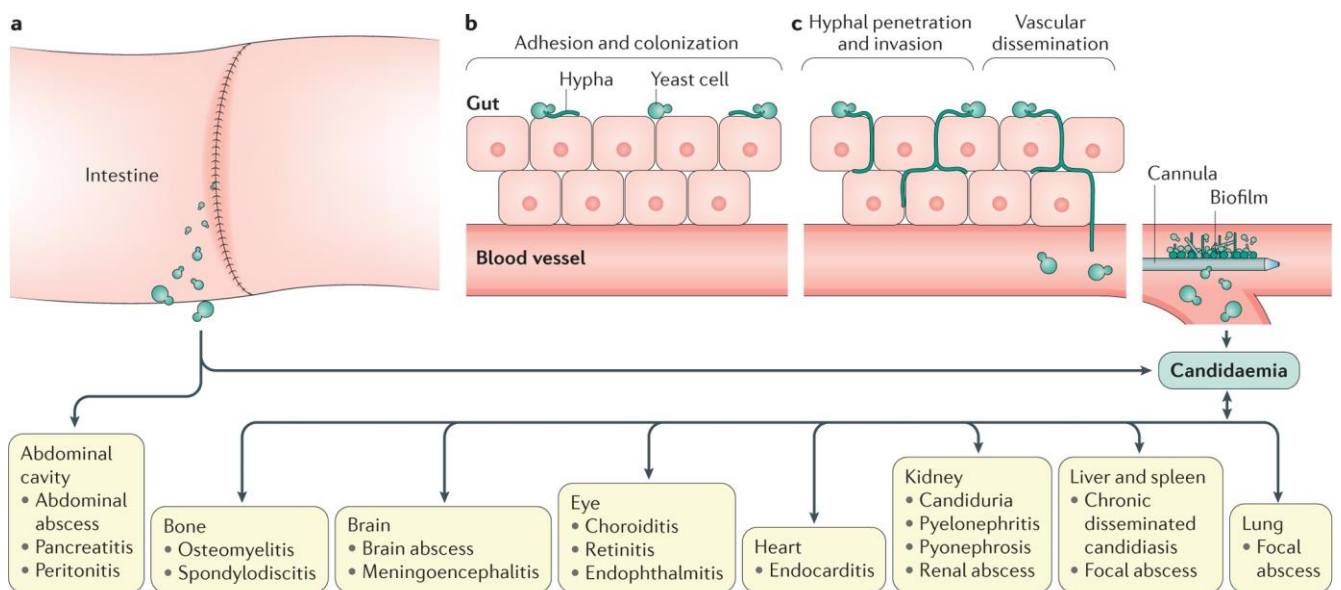
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Vol. 9, Issue 3, March 2020

C. gattii possesses a thick polysaccharide capsule composed of glucurono- and galactoxylomannan, which, analogous to encapsulated bacteria like *Streptococcus pneumoniae*, blocks phagocytosis of the organism unless it is opsonized. Presumably, the dense capsule also provides some protection against hydrolytic enzymes exocytosed by neutrophils. Capsular glucuronoxylo-mannan and other macromolecules, as well as virulence-associated proteins, are carried through the cell wall in an amazing process involving vesicles that originated from the late endosome (multivesicular body). [13,14]

III. DISCUSSION

Other Tremellales parasitize fungi by attaching to the host fungus with a specialized hypha and accessing its cytoplasm through a newly created pore. An evolutionary trajectory from parasitizing another live fungus to parasitizing an animal host may have proceeded through association with and parasitism of insects, and through selection in soils by amoebae for traits that can also function in mammalian virulence. The human-pathogenic *Cryptococcus* species killed larvae of the wax moth *Galleria mellonella* in one study, whereas their Tremellales relatives partially or completely lacked virulence in this insect model. A limited number of species are commonly associated with humans as colonizers and opportunistic pathogens: *C. albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, *Candida lusitanae*, and *Candida krusei*. [15,16]



Nature Reviews | Disease Primers

Invasive candidiasis

Of these, *C. albicans* is the most commonly isolated human commensal and pathogen. Invasive candidiasis takes many forms, depending on the setting in which a host became susceptible to this opportunist, and depletion of normally competing bacterial flora by antibiotics often plays a role. For example, in cancer patients receiving chemotherapy, candidiasis is often caused by fungal transmigration through disrupted intestinal epithelium, and the organs with the heaviest fungal burden are those connected by the portal circulation—liver and spleen—but not the brain. In contrast, premature newborns with candidiasis often have abscesses in the brain, because their blood–brain barrier may be immature and because their brain receives such a large fraction of cardiac blood output.

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Visit: www.ijirset.com

Vol. 9, Issue 3, March 2020



Oral candidiasis

C. albicans is an efficient invasive pathogen, causing mucous membrane infections in individuals with ineffective adaptive cellular immunity and fatal disseminated infections in patients lacking functional innate immune cells, neutrophils. For a microorganism that relies on person-to-person transmission and does not have a significant soil reservoir (or mode of locomotion back from the soil to its primary host), the benefit of multiplying to the point of host death seems mysterious. One idea might be that the *Candida* pathogenic repertoire evolved to take advantage of a constant large number of temporarily susceptible humans, infants, who develop oral candidiasis because of immature adaptive immunity. Human infants' propensity to widely distribute their oral secretions (to slobber) may allow infecting *Candida* to launch its increased numbers from infected mucous membranes of these hosts and to colonize more of their contacts. If this is the case, *Candida* virulence factors evolved to efficiently infect mucous membranes, and invasive disease is for it an accidental dead end.[17]

IV. RESULTS

Aspergillus conidia can give rise to allergic lung disease, and the fungus can colonize the bronchiectasis of cystic fibrosis or chronic obstructive lung disease; but lethal invasive infection occurs when there is a dearth of functional neutrophils and macrophages to control germinating conidia. Hyphae proliferate in lung parenchyma or sinuses, and hyphal fragments occasionally are carried to highly perfused organs like the brain in which they initiate foci of metastatic infection. On encountering blood vessels, *Aspergillus* hyphae tend to enter and follow their course, clogging the vessel and causing infarction of downstream tissue. This angioinvasive behavior may be attributable to thigmotropism, the ability to sense and follow contours, which aspergilli have in common with fungi of diverse phyla. Neutrophils are attracted by the chemokines secreted by resident alveolar macrophages encountering *A. fumigatus* during their patrols of the alveolar space. Whereas small hyphae are engulfed and killed by neutrophils, larger hyphae are killed by their extracellular release of reactive oxygen and nitrogen species and antimicrobial peptides, in dependence on the pathogen recognition receptors (PRRs) TLR2 and 4, and dectin-1.

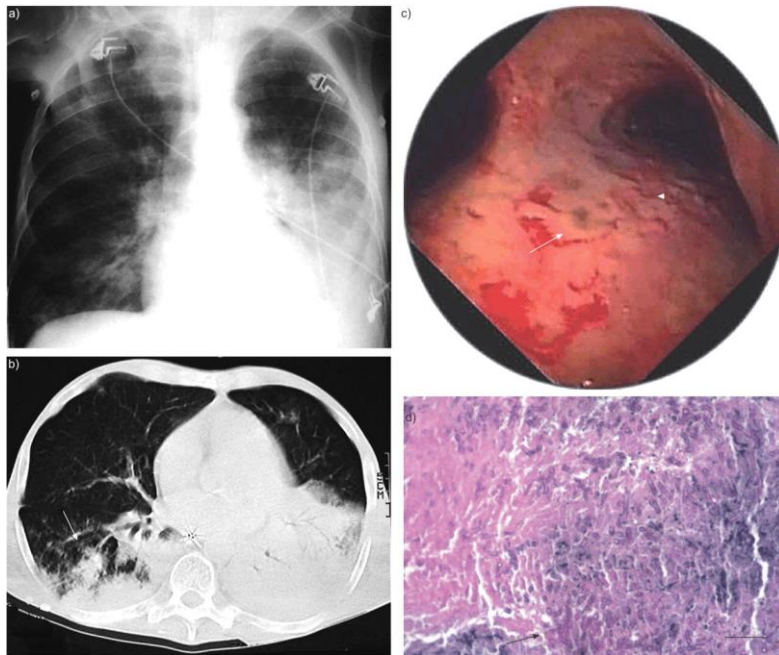
Fusarium spp. have evolved to infect plants, and the genomes of certain lineages contain one or more entire chromosomes encoding plant pathogenicity factors, which may be horizontally transferred within the genus.

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Vol. 9, Issue 3, March 2020



Invasive pulmonary Aspergillosis

Whether possession of a pathogenicity chromosome corresponds to virulence for humans, for instance, in the *F. oxysporum* lineage identified to have caused 70% of invasive fusariosis in a San Antonio hospital, is not yet known. In *Fusarium*, morphogenesis contributes to virulence for humans, because yeast-like cells are produced from hyphae in the host, and typically spread widely through the bloodstream to cause numerous foci of infection in the skin.

Pigmented filamentous ascomycetes, also called dematiaceous fungi, infect immunocompromised and, rarely, immunocompetent individuals to cause phaeohyphomycosis. Their pathobiology is diverse including brain abscesses (*Cladophiala bantianum*, *Ramichloridium* spp., and *Dactylaria gallopava*), keratitis, sinus or soft tissue infections, ulcers, and cysts (*Exophiala jeanselmei*, *Exophiala dermatitidis*, *Curvularia* spp., *Bipolaris*, or *Alternaria* spp.). When directly inoculated into tissue, these fungi can cause devastating disease, as emphasized in a tragic outbreak caused by contaminated injectable steroids.

Basidiomycota

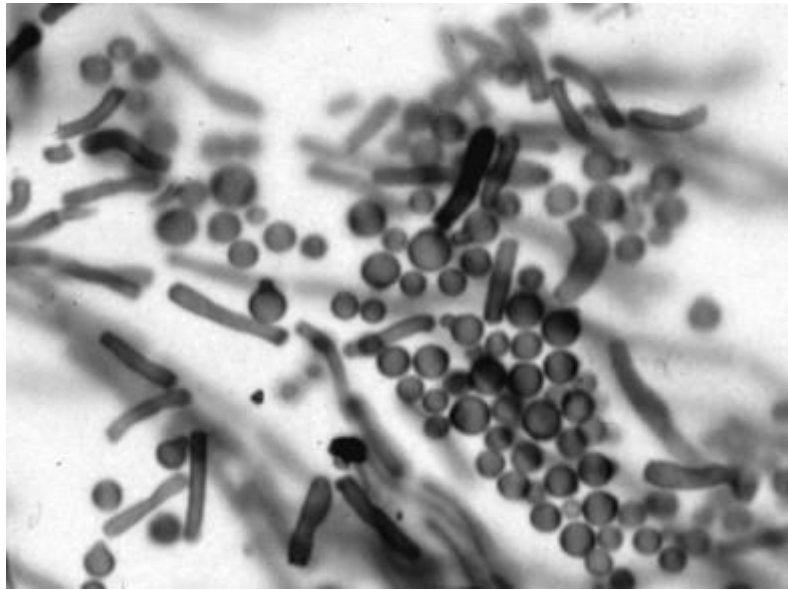
In addition to the *Cryptococcus* spp. discussed above, other Basidiomycota growing predominantly as yeast in the host, *Malassezia furfur*, *Trichosporon asahii*, and other members of human skin flora, are opportunists in patients with venous catheters and in immunosuppressed patients.[18]

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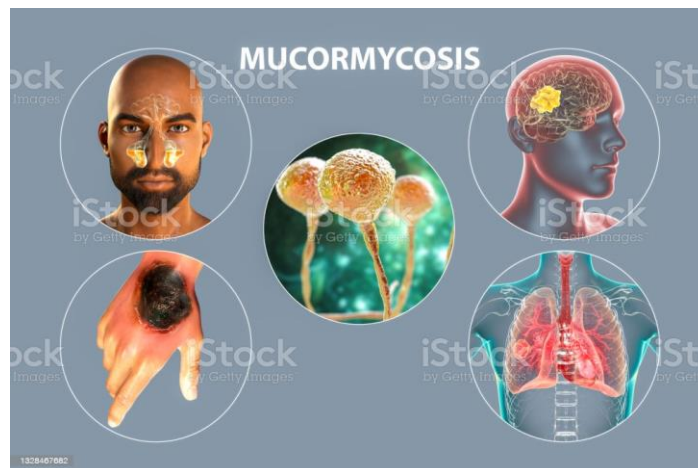
Vol. 9, Issue 3, March 2020



Malassezia furfur

Mucorales

Profoundly immunocompromised patients at risk for the environmental fungi described above are also at risk for Mucorales infections. Additionally, Mucorales cause severe disease in diabetic patients especially at times of uncontrolled blood glucose, and patients with elevated serum iron (e.g., attributed to hemosiderosis), as described in the excellent series. Like the aspergilli, these fungi cause disease where airborne dispersal cells, sporangiospores, enter air-filled spaces (i.e., in sinuses and lungs). Infections with Mucorales progress rapidly as the fungus grows fast and relentlessly through tissue planes and bone, penetrating the eye and the brain when originating in sinuses, and causing widespread infarction because of its angioinvasive behavior. [19]



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Vol. 9, Issue 3, March 2020

V. CONCLUSION

Immunologically intact humans manifest robust defenses against fungal diseases. Recently, human social evolution produced scientific medicine, whose progress has rendered a large population susceptible to infections with fungi not considered human pathogens as recently as a hundred years ago. Human social evolution may have reached a stage where prioritization of the resources needed for understanding fungal biology and for successful development of multiple new classes of antifungals is possible, as the example of AIDS shows. Effective antiretroviral therapy was developed with a massive research effort less than two decades ago, and if human society evolves to a point of valuing all human lives equally, near elimination of AIDS is as feasible as the quasi elimination of HIV mother-to-child transmission has been in wealthy countries. Unlike with HIV, which has no reservoir in nature, humans will always have to cope with fungal infections, because potential fungal pathogens are part of our normal flora and of soil, water, and air. But building on the tremendous efforts and findings of the past decades, new low-toxicity therapies and novel preventative measures of fungal infections can be within our reach.[20,21]

REFERENCES

- 1) Abad A, Fernandez-Molina JV, Bikandi J, Ramirez A, Margareto J, Sendino J, Hernando FL, Ponton J, Garaizar J, Rementeria A 2010. What makes *Aspergillus fumigatus* a successful pathogen? Genes and molecules involved in invasive aspergillosis. *Rev Iberoam Micol* 27: 155–182. [PubMed] [Google Scholar]
- 2) Aimananda V, Bayry J, Bozza S, Knemeyer O, Perruccio K, Elluru SR, Clavaud C, Paris S, Brakhage AA, Kaveri SV, et al. 2009. Surface hydrophobin prevents immune recognition of airborne fungal spores. *Nature* 460: 1117–1121. [PubMed] [Google Scholar]
- 3) Albrecht A, Felk A, Pichova I, Naglik JR, Schaller M, de Groot P, Maccallum D, Odds FC, Schafer W, Klis F, et al. 2006. Glycosylphosphatidylinositol-anchored proteases of *Candida albicans* target proteins necessary for both cellular processes and host–pathogen interactions. *J Biol Chem* 281: 688–694. [PubMed] [Google Scholar]
- 4) Alby K, Schaefer D, Bennett RJ 2009. Homothallic and heterothallic mating in the opportunistic pathogen *Candida albicans*. *Nature* 460: 890–893. [PMC free article] [PubMed] [Google Scholar]
- 5) Ameen M 2010. Epidemiology of superficial fungal infections. *Clin Dermatol* 28: 197–201. [PubMed] [Google Scholar]
- 6) Araujo Gde S, Fonseca FL, Pontes B, Torres A, Cordero RJ, Zancope-Oliveira RM, Casadevall A, Viana NB, Nimrichter L, Rodrigues ML, et al. 2012. Capsules from pathogenic and non-pathogenic *Cryptococcus* spp. manifest significant differences in structure and ability to protect against phagocytic cells. *PLoS ONE* 7: e29561. [PMC free article] [PubMed] [Google Scholar]
- 7) Argimon S, Fanning S, Blankenship JR, Mitchell AP 2011. Interaction between the *Candida albicans* high-osmolarity glycerol (HOG) pathway and the response to human β -defensins 2 and 3. *Eukaryot Cell* 10: 272–275. [PMC free article] [PubMed] [Google Scholar]
- 8) Aulakh HK, Aulakh KS, Troy GC 2012. Feline histoplasmosis: A retrospective study of 22 cases (1986–2009). *J Am Anim Hosp Assoc* 48: 182–187. [PubMed] [Google Scholar]
- 9) Bagagli E, Bosco SM, Theodoro RC, Franco M 2006. Phylogenetic and evolutionary aspects of *Paracoccidioides brasiliensis* reveal a long coexistence with animal hosts that explain several biological features of the pathogen. *Infect Genet Evol* 6: 344–351. [PubMed] [Google Scholar]
- 10) Bagagli E, Theodoro RC, Bosco SM, McEwen JG 2008. *Paracoccidioides brasiliensis*: Phylogenetic and ecological aspects. *Mycopathologia* 165: 197–207. [PubMed] [Google Scholar]
- 11) Bastidas RJ, Heitman J 2009. Trimorphic stepping stones pave the way to fungal virulence. *Proc Natl Acad Sci* 106: 351–352. [PMC free article] [PubMed] [Google Scholar]
- 12) Bauder B, Kubber-Heiss A, Steineck T, Kuttin ES, Kaufman L 2000. Granulomatous skin lesions due to histoplasmosis in a badger (*Meles meles*) in Austria. *Med Mycol* 38: 249–253. [PubMed] [Google Scholar]
- 13) Bergman A, Casadevall A 2010. Mammalian endothermy optimally restricts fungi and metabolic costs. *mBio* 1: e00212–10. [PMC free article] [PubMed] [Google Scholar]

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(A High Impact Factor, Monthly, Peer Reviewed Journal)

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Vol. 9, Issue 3, March 2020

- 14) Beyhan S, Gutierrez M, Voorhies M, Sil A 2013. A temperature-responsive network links cell shape and virulence traits in a primary fungal pathogen. *PLoS Biol* 11: e1001614. [PMC free article] [PubMed] [Google Scholar]
- 15) Bittencourt AL 1988. Entomophthoromycosis. Review. *Med Cutan Ibero Lat Am* 16: 93–100. [PubMed] [Google Scholar]
- 16) Bittencourt AL, Marback R, Nossa LM 2006. Mucocutaneous entomophthoromycosis acquired by conjunctival inoculation of the fungus. *Am J Trop Med Hyg* 75: 936–938. [PubMed] [Google Scholar]
- 17) Blake JS, Dahl MV, Herron MJ, Nelson RD 1991. An immunoinhibitory cell wall glycoprotein (Mannan) from *Trichophyton rubrum*. *J Invest Dermatol* 96: 657–661. [PubMed] [Google Scholar]
- 18) Boelaert JR, de Locht M, Van Cutsem J, Kerrels V, Cantinieaux B, Verdonck A, Van Landuyt HW, Schneider YJ 1993. Mucormycosis during deferoxamine therapy is a siderophore-mediated infection. In vitro and in vivo animal studies. *J Clin Invest* 91: 1979–1986. [PMC free article] [PubMed] [Google Scholar]
- 19) Bohse ML, Woods JP 2007. Expression and interstrain variability of the *YPS3* gene of *Histoplasma capsulatum*. *Eukaryot Cell* 6: 609–615. [PMC free article] [PubMed] [Google Scholar]
- 20) Bounoux ME, Pujol C, Diogo D, Bouchier C, Soll DR, d'Enfert C 2008. Mating is rare within as well as between clades of the human pathogen *Candida albicans*. *Fungal Genet Biol* 45: 221–231. [PMC free article] [PubMed] [Google Scholar]
- 21) Bowen AD, Davidson FA, Keatch R, Gadd GM 2007. Induction of contour sensing in *Aspergillus niger* by stress and its relevance to fungal growth mechanics and hyphal tip structure. *Fungal Genet Biol* 44: 484–491. [PubMed] [Google Scholar]