Chapter 16 Molds of Man

Human and mammalian pathogens

- Pathogenic fungi are grouped based on:
  - Primary route of entry
  - Type of disease they cause
  - Natural sources of inoculum

Human and mammalian pathogens

- Five categories:
  1) Dermatophytes
  2) Commensals
  3) Saprophytes
  4) Pathogens of traumatized tissue
  5) Pneumocystis

Dermatophytes

- Ringworm fungi
  - Grow on dead, keratinized tissues of skin, hair, & nails
    - Shed tissues are source of inoculum
  - Resulting diseases are superficial
    - Secondary invasion by bacteria
  - Persist in dormant phase
    - Cross-infect other hosts

Dermatophytes

- About 40 species
  - Three genera:
    - Trichophyton
    - Microsporum
    - Epidermophyton
- Grow in dead, keratinized tissues of skin, nails, and hair
- Cannot grow at 37°C
**Dermatophytes**

- Metabolic products can induce inflammatory response & cause irritation
  - Enable bacteria to invade
  - Shedding of infested skin and hair
- Indirect transmission

**Pathogenicity and virulence factors**

- Key features that contribute to diseases
  1. Ability to grow on substrates rich in keratin
  2. Host specialization

**Keratinases**

- Breaks down keratin
  - Allow to grow on keratin as sole carbon and energy source
- Could be virulence determinants

**Candida albicans**

- Occurs as a diploid budding yeast
- Found on mucosal membranes of more than 50% of healthy individuals
- Can cause local or systemic infections collectively called candidosis

**Clinical Manifestations of C. albicans**

- If infection occurs in the mouth or throat, it causes speckled white pustules
- Common with newborn children when mother has an infected birth canal
Clinical Manifestations
- Can also be contracted by those wearing dentures or using catheters
- Commonly contracted by those with compromised immune systems
- Infection can also take place when individuals have been on a prolonged course of antibiotics

Virulence Determinants of C. albicans
- Ability to adhere strongly to multiple surfaces
- Ability to undergo a dimorphic switch

Adhesins
- Although many studies have been performed on C. albicans ability to adhere, the precise role of adherence and infection
- Strains collected from those with active infections seem to have a stronger ability to adhere

Adhesins
- Studies have shown that strains of C. albicans grown on sugars such as galactose, maltose, and sucrose show greater ability to adhere to epithelia and denture resin
- C. albicans ability to adhere comes from the use of mannoprotein adhesins in the cell wall

The Dimorphic Switch
- C. albicans normally grows as a budding yeast but in response to nutrient limitation, cells begin to grow hyphae-like outgrowths
- These structures are called pseudohyphae

The Dimorphic Switch
- Difficult to understand how the dimorphic switch is regulated in C. albicans
- Constitutively diploid so it is difficult to obtain mutants
- This particular species has a different codon for serine CUG which is lysine in most other organisms
The Discovery of Mating-Type Genes

- C. albicans was originally thought to reproduce only through asexual budding
- In 1998, one mating type like locus was found
- Since there is only one locus normally mating cannot occur

Opportunistic and Incidental Pathogens

- Theoretically any fungus that grows at 37°C can cause infection
- Actual range of human pathogens are far narrower
- Some fungi infect wounds
- Other fungi are able to infect the lungs because of small spore size

Aspergillosis

- Members of the genus Aspergillus are normally saprotrophs of organic materials
- Produce abundant small conidia that are easily inhaled
- People with impaired respiratory function, colonies called aspergillomas can form in the lungs

Aspergillus fumigatus

- Most dangerous airborne fungal human pathogen
- Can cause infection if spores are inhaled
- Can also enter the body through surgical wounds
- Systemic infection can occur if person is immunocompromised

Systemic infection of C. albicans

- People can develop a systemic infection with certain predisposing factors
- Leukemia, diabetes, corticosteroid therapy
- Systemic infection rarely occurs in AIDS patients
**Virulence Factors of A. fumigatus**
- No specific virulence factors have been found
- All strains seem to be equally infectious

**Endemic Dimorphic Fungi**
- Temperature dependent dimorphic switch
- All enter through the lungs
- Limited to a geographically localized area

**Endemic dimorphic fungi**
- Geographically localized
- Dimorphic: switching forms from temperature shifts
- Infect through airborne spores
- Immunocompromised, individuals prone to lung infections, advanced diabetes and leukemia patients most affected

**Coccidioides immitis**
- Grows in alkaline soils of desert region
  - California, Arizona, Texas, Central and South America
- Produce hyphae at environmental temperature 25°C
- Hyphae fragment to produce small, thick walled spores which are air transported
  - Arthrospores or Arthroconidia

**Coccidioides immitis**
- Spherule in host environment 37°C
- C. immitis and C. posadasii are only dimorphic fungi that produce spherules
- Others produce a yeast-like budding phase

**Coccidioides immitis**
- Spherule to phase in the lungs
- Arthrospores

[Coccidioides immitis diagram](http://www.missionforvisionusa.org/anatomy/2007/02/coccidioidomycosis.html)

**Coccidioides immitis**
- **Coccidioidomycosis** - Causes infection of the bone, subcutaneous tissue, meninges, and major organs.
- "Biologic agent with the potential to pose severe threat to public health and safety that could potentially be used by terrorists."

**Histoplasma capsulatum**
- **Wide geographical distribution**
  - Eastern USA, Latin America, Southeast Asia, Africa, Europe.
- "Typical" mold-yeast dimorphism.
- Hyphae produce single conidia on end.
- Macroconidia and microconidia.

**Histoplasma capsulatum**
- Hyphae involved in saprotrophic phases in dead tissue or in natural substances.
- Saprotrophic in fecal-enriched soil (birds, bats and poultry).

**Histoplasma capsulatum**
- Airborne spores enter lungs infecting host.
- Spores germinates to form germ-tube then budding yeast phase.
- Yeast phase found in infection.

**Histoplasma capsulatum**
- **Histoplasmosis**
  - Fever
  - Headache
  - Dry cough
  - Cough
  - Chest pains
  - Ulcers of the mouth and tongue.

**Blastomyces dermatitidis**
- Found in southeastern and south central USA.
- Associated with moist soil with organic matter or rotting wood.
- In vitro: narrow hyphae with a single globose conidia.
- Transforms into thick-walled yeast-like budding phase.
**Blastomyces dermatitidis**

- Airborne conidia infect lungs
- 50% of infections are asymptomatic
- Acute pulmonary phase after 30-40 day incubation
- Chronic phase affects lungs, skin, bones, gastrointestinal tract, ulcerative lesions, granulomatous inflammation of lungs

**Paracoccidioides brasiliensis**

- Subtropical forest regions
  - Central and South America
- Mitosporic fungus with no sexual stage
- Grows as mycelia at lower temperature and as budding yeasts at host temperature

**Cryptococcus neoformans**

- The only human pathogen out of 30 yeast Cryptococcus species
- Causes a disease called "cryptococcosis"
- Initially a rare disease
  - Naturally Immunosuppressed people
  - Patients undergone surgeries

**Blastomyces dermatitidis**

  - Thermally regulated dimorphism is single most defining trait
  - Linked to phase-specific gene termed BAD1 (Blastomyces adherence)
  - Found in yeast phase not in hyphal phase that grow in lower temperatures
  - Yeast phase cells consist of 90% α-glucan, mycelial phase cells equal centers α-glucan and β-glucan
  - Reduced content of α-glucan correlates with loss of virulence
**Cryptococcus neoformans**
- Increase in HIV/AIDS has caused increase in Cryptococcosis cases.
- 7-10% HIV/AIDS are affected by *C. neoformans* worldwide.
- Route of infection is via inhaling spores or yeast cells.

**Cryptococcosis symptoms**
- Causes an initial subclinical pulmonary infection.
- Chronic lung infection with a primary lesion in the lung.
- Disseminate to the central nervous system
  - Major growth in the cerebral cortex, brain stem, cerebellum, and meninges.

**The fungus *C. neoformans***
- A haploid yeast. Diameter 2.5 to 10μm.
- Dehydrated yeast cells are the primary cause of infection.
- Small cells reach the alveoli, rehydrate and cause infection.
- Production of airborne basidiospores (1.8-3.0μm)

**The fungus *C. neoformans***
- Basidiospores produced by mating types “a” and “α” cultured on a water-stressed and nitrogen lacking media.
- Two varieties;
  - *C. neoformans var. neoformans*
  - *C. neoformans var. gattii*

**Pathogenicity and Virulence determinants of *C. neoformans***
- Pathogenic determinants- Factors that enable invasive organism to live in a host environment
  - Grow at 37°C, 5% CO2, and pH of ~7.3.
  - Gene coding for calcineurin A
    - Protein phosphatase activated by Ca2+ calmodulin.
    - Involved in stress responses in yeasts.
    - Mutants with defective calcineurin A cannot grow in the above mentioned conditions.

**Virulence Determinants**
- Factors that determine the severity of the disease.
  - Presence of a thick, rigid polysaccharide capsule around yeast cells that are not easily phagocytized or killed.
  - Brown or black pigments containing phenolic compounds, produce melanin to protect against reactive oxidants.
Pneumocystis species
- Worldwide distribution among different host-specific species with no cross-infection
- Primitive fungus-like organism
- Life cycle closest to Protozoa (protist) and placed usually along the early ascomycota
- The only fungus that has cholesterol instead of ergosterol in the cell membrane
- Infects many species of mammals including humans

Pneumocystis
- Causes Pneumocystis carinii pneumonia (PCP) or pneumonitis
- Common cause of death in AIDS/immunocompromized patients
- Strongly age linked infection

Modes of transmission, pathology, & life cycle of Pneumocystis
- Some environmental samples detected as airborne spores and pond water
- Major sources of infection:
  - Activation of pre-existing latent infection
  - Re-infection from inhaled spores
- Lung infection established in the alveoli type 1 epithelial cells
- Direct correlation with a low number of CD4+ lymphocytes

Complicated life cycle
- Asexual trophic forms proliferate in the lungs
- Sexual stage involves conjugation of haploid cells to form a diploid “pre-cyst”
  - The precyst undergoes meiosis and mitosis to form a eight haploid nucleus called the “late phase cyst”
- These cysts can proliferate upto 4 layers of alveolar lumen creating oxygen deficiency
- Advanced stages in major organs like lymph nodes, bone marrow, liver and spleen.

Conclusions
- In humans, children are the primary reservoir of infections.
- Discovery of polymorphism of genes has led to investigations for epidemiology of human infections due to pneumocystis.

Questions
- Which is NOT a feature used to group human-pathogenic fungi?
  - A. Primary route of entry
  - B. Type of disease they cause
  - C. Temperature tolerance
  - D. Natural sources of inoculum
**Questions**

Which is NOT one of the three genera of dermatophytes?
A. *Trichophyton*
B. *Absidia*
C. *Microsporum*
D. *Epidermophyton*

**Questions**

Localized saprotrophic colonies in the lungs caused by *A. fumigatus* are called:
A. Carcinomas
B. Aspergillomas
C. Stomatitis
D. Cysts

**Questions**

True or False, *Candida* often cause systemic infection in AIDS patients.

**FALSE**
C. albicans rarely causes systemic infection in AIDS patients, other systemic fungal infections tend to develop instead.

**Questions**

True or False

You can get these fungal infections from an infected person.

**FALSE**
Once the disease is established in the body it has transformed to the yeast form (or spherule in *C. immitis*), which is not infectious.

**Questions**

The reduction of which cell wall component in yeast cells correlates with loss of virulence in animal models based on Brandhorst et al?
A. β-glucan
B. Chitin
C. α-glucan
D. Ω-glucan
True or False
The major pathogenic determinants for *C.neoformans* are being able to grow at 37°C, in atmosphere of about 5% CO2 and at a pH of 7.3.

FALSE

The Pneumocystis species have a life cycle that resembles which one of the following most closely?
A. *Coccidioides immitis*
B. Virus
C. *C.neoformans*
D. Protozoa