FUNGAL DISEASES

The fungal kingdom encompasses a diverse and rich group of organisms ranging from microscopic yeasts to mushrooms. Around 90,000 known fungal species, out of which approx. 200 have been reported to produce disease in humans. Study of fungi is known as Mycology. The fungal cell has many typical eukaryotic features, that includes nucleus, ribosomes, mitochondria, endoplasmic reticulum and Golgi apparatus. Fungal cells have a rigid cell wall external to the cytoplasmic membrane, which differs in its chemical composition from the cell walls of bacteria and plants. Ergosterol, not cholesterol, makes up cell membrane. The chemical structure of the cell wall in fungi is composed of mannans, glucans, and chitins in close association with each other and with structural proteins. The size of fungi varies immensely. A single cell without transverse septa may range from bacterial size (2-4 μm) to a macroscopically visible structure.

REPRODUCTION

Fungi may reproduce by either asexual or sexual process. The asexual form is called the anamorph, and its reproductive elements are termed conidia (formed by mitosis). The sexual form is called the teleomorph, and its reproductive structures formed by meiosis are called spores (e.g., ascospores, zygospores, basidiospores).

Fungi that cause human infections can be broadly divided based on their morphological forms: Yeasts and Molds. Yeasts are fungi that primarily grow in a round cellular form. Molds are fungi that primarily grow as filamentous, tube-like structures called hyphae.

Some species can transit between morphological forms depending on environmental conditions such as temperature. These species are known as dimorphic fungi. *e.g., Candida albicans.*

Groups of medically important fungi:

- Superficial fungi, such as the dermatophytes, cause indolent lesions of the skin and its appendages, commonly known as ringworm and athlete’s foot, without typically spreading to deeper tissues.
- Subcutaneous pathogens characteristically cause infection through the skin, followed by subcutaneous or lymphatic spread.

- Opportunistic fungi are those found in the environment or in the resident flora that produce disease primarily in immunocompromised hosts.
- Systemic pathogens are the most virulent fungi and may cause serious and progressive systemic disease in previously healthy persons.

Adherence usually requires a surface adhesin on the fungus and a receptor on the epithelial cell. In the case of *C albicans*, mannoprotein components extending from the cell wall have been implicated as specific adhesins, interacting with host fibronectin and other components of the extracellular matrix.

Innate Immunity: Healthy persons have effective innate immunity to most fungal infections, especially the opportunistic molds. This resistance is mediated by the professional phagocytes (neutrophils, macrophages, and dendritic cells), the complement system, and pattern recognition receptors. Important receptors recognizing fungal elements include a lectin-like structure on phagocytes (dectin-1) that binds glucan, and toll-like receptors (TLR2, TLR4).

LABORATORY DIAGNOSIS

- Direct Examination Fungi can often be identified by directly observing their distinctive morphologic features on direct microscopic examination of infected pus, fluids, or tissues. The simplest method is to mix a clinical specimen, such as skin scrapings, with a 10% solution of potassium hydroxide (KOH) on a microscope slide under a coverslip. The strong alkali digests the tissue elements (epithelial cells, leukocytes, debris), but not the rigid cell walls of either yeasts or molds. After digestion of the material, the fungi can be observed under the light microscope with or without staining.
- Some yeasts are gram positive. Therefore, they can be stained with Gram’s stain.
- Fungi often visible in Hematoxylin & Eosin preparations.
- Silver stain can also be used as it enhance detection.
- Growth in culture is another simple method but it is slow.
- Selective media allow isolation in the presence of bacteria.
- Temperature variation can be used to demonstrate dimorphism.
- DNA probes are more rapid way of detection.
- Antigen and Antibody Detection: Serum antibodies directed against a variety of fungal antigens can be detected in patients infected with those agents. Immunoassays

to detect fungal antigens have been pursued for some time. The major targets are mannans, mannoproteins, glucan, chitin, or some other structure unique to the fungal pathogen(s).

ANTIFUNGAL AGENTS

CYTOPLASMIC MEMBRANE

- Polyenes

The polyenes **nystatin and amphotericin B** are lipophilic and bind to ergosterol, the dominant sterol in the cytoplasmic membrane of fungal cells. After binding, they form annular channels, which penetrate the membrane and lead to leakage of essential small molecules from the cytoplasm and cell death. Their binding affinity for the ergosterol of fungal membranes is not completely specific, cross-reacting with mammalian sterols such as cholesterol. This is the basis for the considerable toxicity that limits their use.

At physiologic pH, amphotericin B is insoluble in water and must be administered intravenously as a colloidal suspension. It is not absorbed from the gastrointestinal tract.
Side effects: chills, fever, headache, and dyspnea. The most serious toxic effect is renal dysfunction, observed in virtually every patient receiving a prolonged therapeutic course.

- Azoles

The azoles are a large family of synthetic organic compounds (e.g., **Fluconazole**), which includes members with antibacterial, antifungal, and antiparasitic properties. Their activity is based on inhibition of the enzyme (14 α-demethylase) responsible for conversion of lanosterol to ergosterol, the major component of the fungal cell membrane. This leads to ergosterol depletion and lanosterol accumulation, forming defective membranes. All antifungal azoles have the same mechanism of action. Less toxic than amphotericin B.

- Allylamines

The allylamines are a group of synthetic compounds that act by inhibition of an enzyme (squalene epoxidase) in the early stages of ergosterol synthesis. The allylamine group includes an oral and topical agent, terbinafine used in the treatment of dermatophyte (ringworm) infections.

NUCLEIC ACID SYNTHESIS

Flucytosine: 5-Flucytosine (5FC) is an analog of cytosine. It is a potent inhibitor of RNA and DNA synthesis. 5FC requires a permease to enter the fungal cell, where its action is not direct

but through its enzymatic modification to other compounds (5-fluorouracil, 5-fluorodeoxyuridyic acid, 5-fluoruridine). These metabolites then interfere with DNA synthesis and RNA transcription.

CELL WALL SYNTHESIS

Echinocandins: act by inhibition of a glucan synthetase (1,3-β-D-glucan synthetase) required for synthesis of the principal cell wall glucan of fungi.

Nikkomycins: Inhibits chitin synthesis.

Other Antifungal Agents

Griseofulvin is a product of one of the Penicillium species of molds. Griseofulvin is actively taken up by susceptible fungi and acts on the microtubules and associated proteins that make up the mitotic spindle. It interferes with cell division and possibly other cell functions associated with microtubules. Griseofulvin is absorbed from the gastrointestinal tract after oral administration and concentrates in the keratinized layers of the skin. It is active only against the agents of superficial mycoses.

Potassium iodide is the oldest known oral chemotherapeutic agent for a fungal infection. It is effective only for cutaneous sporotrichosis. Its activity is somewhat paradoxical, because the mold form of the etiologic agent, *Sporothrix schenckii*, can grow on medium containing 10% potassium iodide. The pathogenic yeast form of this dimorphic fungus appears to be susceptible to molecular iodine.

MECHANISMS OF RESISTANCE

Polyene Resistance: Because amphotericin B binds directly to the ergosterol in the fungal cell membrane, the only means to resist this action is to change the membrane sterol composition. Therefore, only a few rare fungal species are intrinsically resistant to amphotericin B.

Flucytosine Resistance: Flucytosine (5-FC) requires a permease for entry into the cell and then multiple enzymes to modify it to the active metabolites that inhibit nucleic acid synthesis. Mutation in any one of these enzymes renders the drug ineffective. This happens readily under the selective pressure of 5-FC use. It is one of the few antimicrobials in which emergence of resistance is predictable during therapy of an acute infection. This is the reason that its use is mostly limited to combination therapy with other antifungals.

Azole Resistance: Azole pumped out by efflux pumps or Demethylase enzyme upregulated or bypassed.