Introduction

Mycology is the study of fungi and their multiple functions in nature. Fungi are microorganisms in the domain eucarya. They show less differentiation than plants, but a higher degree of organization than the prokaryotes bacteria (Table 1). The kingdom of the fungi (Mycota) comprises over 50 000 different species, only about 200 of which have been identified as human pathogens (human mycoses). Many mycotic infections are relatively harmless, for instance the dermatomycoses. In recent years, however, the increasing numbers of patients with various kinds of immune defects have resulted in more life-threatening mycoses.

Table 1: Comparison between fungi and bacteria

No.	Properties	Fungi	Bacteria
1	Nucleus	Eukaryotic; nuclear membrane; more than one chromosome; mitosis	Prokaryotic; no membrane; nucleoid; only one “chromosome”
2	Cytoplasm	Mitochondria; endoplasmic reticulum; 80S ribosomes	No mitochondria; no endoplasmic reticulum; 70S ribosomes
3	Cytoplasmic membrane	Sterols (ergosterol)	No sterols
4	Cell wall	Glucans, mannans, chitin, chitosan	Murein, teichoic acids (Gram-positive), proteins

Classification

The Classification of the fungi is essentially based on their morphology. In medical mycology, fungi are classified according to practical aspects as **yeasts, molds, and dimorphic fungi**. Molds grow in filamentous structures, yeasts as single cells. Dimorphic fungi can appear in both of the two forms, as yeast cells or as mycelia .

Fungi are carbon heterotrophs. The saprobic or saprophytic fungi take carbon compounds from dead organic material whereas biotrophic fungi (parasites or symbionts) require living host organisms. Some fungi can exist in both saprophytic and biotrophic forms.

Morphology

Morphological forms of fungi are observed (Fig. 1):

Hypha: this is the basic element of filamentous fungi with a branched, tubular structure, 2–10 μm in width.

Mycelium: this is the web or mat like structure of hyphae. Substrate mycelia (specialized for nutrition) penetrate into the nutrient substrate, whereas aerial mycelia (for asexual propagation) develop above the nutrient medium.

Fungal thallus: this is the collected of the mycelia and is also called the fungal body or colony.

Yeast: the basic element of the unicellular fungi. It is round to oval and 3–10 μm in diameter. Several elongated yeast cells chained together and resembling true hyphae are called pseudohyphae .

Dimorphism: some fungal species can develop either the yeast or the mycelium form depending on the environmental conditions, a property called dimorphism. Dimorphic pathogenic fungi take the form of yeast cells in the parasitic stage and appear as mycelia in the saprophytic stage .

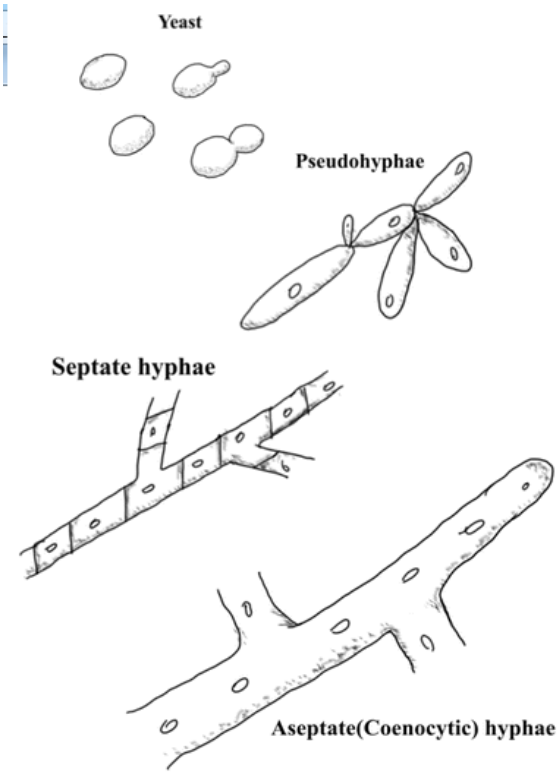

Figure 1: Morphology of fungi

Reproduction in Fungi

A. Asexual reproduction. This includes the vegetative propagation of hyphae and yeasts as well as vegetative fructification, i.e., formation of asexual spores .

1. Hyphae elongate in a zone just short of the tip in which the cell wall is particularly elastic. This apical growth process can also include formation of swellings that develop into lateral hyphae, which can in turn also branch out .
2. Yeasts reproduce by budding. This process begins with an outgrowth on the mother cell wall that develops into a daughter cell or blastoconidium. The isthmus between the two is finally cut off by formation of a septum. Some yeasts propagate in both the yeast and hypha forms .
3. Vegetative fructification. A type of propagative form, the asexual spores, is formed in this process. These structures show considerable resistance to exogenous noxae and help fungi spread in the natural environment. Asexual spores come in a number of morphological types: conidia, sporangiospores, arthrospores, and blastospores. These forms rarely develop during the parasitic stages in hosts, but they are observed in cultures. The morphology of the asexual spores of fungi is an important identification characteristic .

B. Sexual fructification. Sexual reproduction in fungi perfecti (eumycetes) follows essentially the same patterns as in the higher eukaryotes. The nuclei of two haploid partners fuse to form a diploid zygote. The diploid nucleus then undergoes meiosis to form the haploid nuclei, finally resulting in the haploid sexual spores: zygospores, ascospores, and basidiospores. Sexual spores are only rarely produced in the types of fungi that parasitize human tissues .

Sexual reproduction structures are either unknown or not present in many species of pathogenic fungi, known as fungi imperfecti (deuteromycetes).

Mycoses

Mycosis (plural Mycoses) is an infectious disease caused by pathogenic fungus in humans and animals. Mycoses are common and a variety of environmental and physiological conditions can contribute to the development of fungal diseases. Inhalation of fungal spores or localized colonization of the skin may initiate persistent infections; therefore, mycoses often start in the lungs or on the skin.

Fungal infections or mycoses cause a wide range of diseases in humans. Mycoses range in extent from superficial infections involving the outer layer of the stratum corneum of the skin to disseminated infection involving the brain, heart, lungs, liver, spleen, and kidneys. The range of patients at risk for invasive fungal infections continues to expand beyond the normal host to encompass patients with the acquired immunodeficiency syndrome; those immunosuppressed due to therapy for cancer and organ transplantation, and those undergoing major surgical procedures. Each of these patient populations has a high risk of developing invasive fungal infections. As the population at risk continues to expand so also does the spectrum of opportunistic fungal pathogens infecting these patients also continue to increase. Many of the deeply invasive mycoses are difficult to diagnose early and often difficult to treat effectively. The development of new approaches to diagnosis and treatment of invasive fungal infections is the subject of intensive research.

Classification of Mycoses

The clinical nomenclatures used for the mycoses are based on the (1) site of the infection, (2) route of acquisition of the pathogen, and (3) type of virulence exhibited by the fungus.

1. Classification Based on Site

Mycoses are classified as superficial, cutaneous, subcutaneous, or systemic (deep) infections depending on the type and degree of tissue involvement and the host response to the pathogen.

Superficial mycoses are limited to the stratum corneum and essentially elicit no inflammation. Cutaneous infections involve the integument and its appendages, including hair and nails. Infection may involve the stratum corneum or deeper layers of the epidermis. Inflammation of the skin is elicited by the organism or its products. Subcutaneous mycoses include a range of different infections characterized by infection of the subcutaneous tissues usually at the point of traumatic inoculation. An inflammatory response develops in the subcutaneous tissue frequently with extension into the epidermis. Deep mycoses involve the lungs, abdominal viscera, bones and or central nervous system. The most common portals of entry are the respiratory tract, gastrointestinal tract, and blood vessels.

2. Classification Based on Route of Acquisition

Infecting fungi may be either exogenous or endogenous. Routes of entry for exogenous fungi include airborne, cutaneous or percutaneous. Endogenous infection involves colonization by a member of the normal flora or reactivation of a previous infection.

3. Classification Based on Virulence

Fungi may be classified also according to virulence, as primary pathogens or as opportunistic pathogens. A primary pathogen can establish infection in an immunologically normal host; whereas, an opportunistic pathogen requires some compromise of host defenses in order for infection to become established.

- There are four types of mycotic diseases:
  A. Hypersensitivity: allergic reaction to molds and spores
  B. Mycotoxicoses: poisoning of man/animals by feeds/ products contaminated by toxin producing fungi
  C. Mycetismus: Ingestion of pre-formed toxins (Mushroom poisoning)
  D. Infections: Mycoses

Host–Fungi Interaction: The Process of Infection

Like any other microbial pathogen, fungal infection also involves some basic steps such as (1) entry and adherence to the host tissue, (2) invasion of the host tissue، (3)multiplication, colonization and dissemination in the tissues, and (4) evasion of the host immune system and damage to the tissues.

1. Entry or Adherence to the Host Tissue

Humans are first exposed to fungus *Candia albicans* when passing through the vaginal canal during birth. In this course the fungus colonizes the buccal cavity, and upper and lower parts of the gastrointestinal tract of the newborn, where it becomes commensal.

Other fungi of human diseases come from exogenous sources of soil and decaying vegetation as saprophytes. Generally, they enter through respiratory portals. Fungi rarely cause disease in immunocompetent hosts, though often exposed to infectious spores. Disease results when fungi accidentally penetrate host barriers or when immunologic defects or other debilitating conditions exist that favor fungal entry and growth.

Infection of a host starts with the adherence of fungi at epithelial surface layers and further dissemination to different host sites. Invasion of various tissues and resistance to attack by the host immune system is necessary for a pathogen to establish infection.

2. Adaptation and Propagation

For a fungus to survive in its niche it has to adapt to constantly changing parameters. Therefore, fungi respond to change in a specific environmental component by inducing transcriptional and translational changes that promote survival under the newest environmental conditions.

When fungi enter the mammalian host their lifestyle changes from saprophytic to parasitic. As saprophytes, fungi survive in an environment with a moderate ambient temperature and pH, essential nutrients such as carbon and metal ions, and atmospheric concentrations of carbon dioxide and oxygen. Once having invaded a human host, these environmental factors are suddenly replaced by drastic changes. In the different niches of a host, completely different nutrient compositions may exist and specialized features of fungal pathogens may be involved in the establishment, dissemination, and manifestation of an infection.

For example, ambient temperature is replaced by the high temperature of the human body. Fungal survival at the elevated temperature of a human host is essential for virulence. The fungal pathogens *Cryptococcous neoformans* and *Aspergillus fumigatus* are simply better able to survive at 37°C□C than their nonpathogenic counterparts.

Fungi often develop morphogenetic virulence mechanisms, e.g., formation of yeasts, hyphae, and spherules that facilitate their multiplication within the host at higher temperature. Yeast cells of many *Candida* species form filamentous pseudohyphae and hyphae in tissues, whereas *C. neoformans* yeasts become coated with a capsule, and *Coccidioides immitis* develops swollen, septated spherules in the host. Other fungi such as *Histoplasma capsulatum*، *Blastomyces dermatitidis*, and *Penicillium marneffei* form filamentous mycelia in the environment, but convert to yeast morphology upon contact with the human host (dimorphic fungi). Hyphae that grow in the skin or nail as dermatophytes can fragment into arthroconidia or other conidial types. On the other hand, ambient pH is replaced with acidic conditions of mucosal surfaces or neutral to slightly alkaline pH of blood and tissues. One pathway used by fungi in response to changing pH involves activation of the transcription factors such as PacC in *A. nidulans* and Rim101 in *C. albicans*. Carbon and metal ions are lacking in host tissues; iron is sequestered from microbes by iron carrier proteins in tissues, creating an iron-limited environment. In order to survive، fungi encode certain mechanisms by employing siderophores, high affinity iron chelators, to efficiently bind host iron into fungal cytoplasm.

Also, fungi have to face hypoxia and high levels of carbon dioxide in tissues. In *C. albicans*, the response to hypoxia is dependent on coordination of specific transcriptional regulators; for example, transcription factor Ace2 represses oxidative metabolic processes and promotes filamentation .

All these specialized adaptations help fungi in sustaining infection at the host site. Most of the free-living pathogenic fungi possess an extremely versatile metabolism which allows them to adapt immediately to changes in the environmental conditions during life in the soil. Therefore, success of infection depends on rapid adaptation to changing micro-environments.

3. Dissemination

Dissemination of fungi in the host body is facilitated by severe endocrinopathies and immune disorders. A fungus utilizes various mechanisms to deceive or destroy the immune cells and spread to various organs. Dissemination depends on interactions of factors from host and fungi.

a. Host Factors

Considering the interaction between host and pathogen, immune cells are the major antagonists to the survival of fungal pathogens inside the host. However, primary resistance to fungal invasion and colonization is contributed by cutaneous and mucosal physical barriers. The non-specific host defenses include (1) the antifungal activity of saliva and sweat, (2) the competition for space and nutrients by the normal microbiota of the skin and mucous membranes, which limits the growth of potential pathogens, and (3) the mechanical barrier of the skin and mucous membranes which prevent entry of fungi.

Inflammatory systems to combat fungal proliferation involving the action of neutrophils, mononuclear phagocytes, and other granulocytes are also considered to be nonspecific. The specific host defenses or acquired immunity consist basically of the cell-mediated immunity regulated by T-lymphocytes. In humans, mycoses acquired by exposure to fungal spores through the respiratory tract are checked primarily by the first line of defense, i.e., mucociliary clearance. Remaining spores are ingested and killed by monocytes or macrophages through phagocytosis as adaptive innate immunity. In addition, healthy individuals employ a second line of defense formed by neutrophilic granulocytes. They mainly attack hyphae, which are too large for ingestion. These in turn are killed by oxidative and non-oxidative mechanisms، including different defenses. Each of these two defense systems alone is able to protect the host against large spores over long time periods.

Fungal pathogens can cause invasive disease only if both protective lines are surpassed.(Overall, severity of disease depends on factors such as inoculum size of the attacking pathogen, magnitude of tissue damages, ability of fungi to multiply in the tissue, and the immune status of the host cells.

b. Fungal Factors

Production of extracellular enzymes such as keratinases, collagenases, gelatinases، phospholipases, lipases, and acid proteinases by dermatophytes, *Aspergillus* sp، *Candida* sp, and *Cryptococcus* sp is considered to be the fungal

associated factor that helps fungi in nutrient uptake, tissue invasion, adherence, and dissemination inside the host. In some fungi such as *C. neoformans*, the presence of capsule may be an important factor. Similarly, the ability to grow at 37^{o}C, dimorphism, and other factors contribute to fungal pathogenesis, which involves a complex interplay of many fungal and host factors.

Virulence and Pathogenicity

Pathogenesis is the ability of a microorganism to infect the host and produce disease resulting from interaction of pathogen with host via expression of certain factors on both sides. Pathogenicity of a fungus depends on its ability to adapt to the tissue environment and to withstand the lytic activity of the host's defenses. Several determinants including genes or gene products such as enzyme molecules known as virulence factors are involved in this relationship, producing superficial to invasive infections in humans. Virulence refers specifically to a property of the pathogen and, according to modern definitions, **virulence is the ability of a pathogen to multiply and cause harm to its host**.

For a fungus to produce disease in a patient, it must be actively invading tissues. Diseases caused by fungi without invasion of live tissues include mould allergies and cutaneous dermatophyte infections (ringworm), in which fungi invade and damage only the nonviable epidermis. Further, potentially lethal mycoses involving deep tissues result from fungal dissemination and invasion throughout the body.

Many human fungal pathogens are dimorphic (capable of reversible transitions between yeast and hyphal forms), and the morphogenetic transition between these forms is often stimulated by growth in the host and correlated with host invasion. However, the nature of association between fungal morphogenesis and host invasion is a highly debated aspect of fungal virulence.

Determinants of pathogenicity are called virulence factors. Pathogenic microbes often possess a number of virulence factors and mechanisms. These factors determine whether the organism (the host) lives or dies during host–microbe interactions.

The factors can be inducible or constitutive, the direct product of genetic elements (proteins), or the products of complex biosynthetic pathways such as polysaccharides or lipid mediators. The virulence factor can be assessed by comparing biological response in fungi with and without the factor. The most convincing evidence for a factor to be considered as a virulence determinant is

the simultaneous loss of the factor and loss of virulence, and the regaining of virulence when the factor is restored. Virulence factors must help the pathogen to grow at elevated temperatures, facilitate adherence, penetration and dissemination, or assist in resistance against innate immune defenses, e.g., phagocytosis and complement، evasion from adaptive immune defenses, or nutritional and metabolic factors، necrotic factors, or morphology variation. The ability of a fungus to grow at 37^{o}C and physiological pH is a virulence factor for fungi that invade deep tissue, and the transition to parasitic form is essential for the pathogenicity of dimorphic fungi.

A size compatible with alveolar deposition is a virulence factor for fungi producing infections by inhalation of airborne spores. Some kinds of virulence factors are commonly required for all pathogens, such as the ability to recognize and adhere to host tissues, to respond rapidly to changes in the external environment and to secrete hydrolases; all are thought to be important in virulence. But the complex nature of the host–fungus interaction has resulted in some factors that are absolutely required for fungal virulence. Some properties are frequently associated with pathogenesis across all fungal pathogens and others have been found to be important for specific pathogens. Because pathogenesis is complex phenomenon, possession of a single putative virulence factor is not sufficient for a fungus to become pathogenic; rather, a complex combination of properties is usually required. Several kinds of processes are thought to be involved in virulence in a wide range of fungal pathogens.