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Fungi-An Overview

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Abstract

Fungi are eukaryotic, non-photosynthetic organisms. Most of the fungal organisms are saprophytic or commensals but some are parasitic as well, causing a myriad of diseases in animals and humans. Some of the fungal organisms are of zoonotic significance and hence can be transmitted from animals to humans. Fungal infections are chronic in nature and only few antifungals are available till date. Risk of fungal infection increases if the indivisual is immunocompromised, suffering from metabolic diseases, old aged and is undergoing prolonged antibiotic therapy. Antifungals are drugs aimed to treat fungal infections. These target the fungal cell, cell membrane, metabolism, nucleic acid, growth and divisions. But as fungi are eukaryotic organisms, antifungals aimed to kill the fungal organism can also potentially harm the host cell.

Keywords: Antifungals; Fungal diseases, Fungal nutrition and culture media, Zoonosis.

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Introduction

Fungi are eukaryotic, non-photosynthetic, slow growing, strictly aerobic chemoorganotrophic, unicellular (yeast) or multicellular (moulds) organisms under the kingdom Fungi in Whittaker's Classification system. Fungal organisms are mostly saprophytes or commensals while some are parasitic as well. They are often acid tolerant and can grow at an acidic p H as well, although the optimum p H for growth is 6 and temperature is 20-30 degree. The cell wall of fungi is made up of chitin. Yeasts are oval, unicellular organisms. Candida albicans and Coccidia immitis are some of the examples of yeast. Moulds are generally filamentous with branching filaments or hyphae like Aspergillus. Some fungi exist in a dimorphic form as well i.e they can exist both as yeast and mould like Histoplasma, Blastomyces, and Cryptococcus etc. Yeast form is seen in infected indivisual or in enriched media at around 37 degree C whereas mould form is seen in environment or when grown at 25 degree C. Fungal toxins are neither exotoxin nor endotoxin in nature rather these are the metabolic byproduct of the fungi responsible for causing mycotoxicosis. One common example is aflatoxicosis. Some fungi form Pseudohyphae in the animal tissue like Candida albicans. Pseudohyphae are yeast like budding structures unseparated from the mother cell. Some of the characters shared by fungi with the animals are mode of nutrition, storing nutrients in the form of glycogen rather than starch. Some of the characteristics shared with plants are, sessile nature, presence of cell wall, chitin, glucans, xylans and mannans in their cell wall, presence of vacuoles etc, but fungi are considered more animal like than plants.

Classification of fungi

Fungal classification is governed by ICBN, Indian Council of Botanical Nomenclature. They are classified on the basis of morphology, spore characteristics, mode of nutrition etc. Fungi can be classified based on the reproductive characteristics into five phyla called Chytridomycota, Zygomycota,

Ascomycota, Basidiomycota, and Deuteromycota. Chytridomycetes are the primitive fungi with some members having cellulose in their cell wall along with chitin. Zygomycota are also called conjugated fungi. It includes the bread mould, Rhizopus and Mucor. These have coenocytic hyphae. Ascomycota are the sac fungi. Ascospores are the sexual spores in a sac like structure (ascus is the Greek word for sac). Morels, truffles, yeasts, Candida, Claviceps, Penicillium, and Aspergillus are some of the important fungi under the Phylum Ascomycota. Basidiomycota are the club fungi that include the edible mushrooms, toadstools, rusts and smut etc. Deuteromycota are the imperfect fungi. Sexual mode of reproduction is absent in these fungi. When sexual stage is discovered in any fungi imperfecti, they are transferred to Ascomycetes. The asexual state is called anamorph and the sexual state is called telomorph. Telomorph of Cryptococcus neoformans is Filobasidiella neoformans. Phylum Ascomycota together with Basidiomycota forms the Dikarya.

Fungal Nutrition and Culture Media

Most of the fungi grow on media rich in carbohydrate such as Potato Dextrose Agar, Malt extract Agar, Cornmeal Agar. Preferred carbohydrates used by the fungus are xylose, glucose, sucrose but they can also use insoluble carbohydrates like cellulose, hemicellulose and lignin from wooden barks for their carbohydrate requirement. They do so by secreting depolymerising enzymes. As the fungi have to defend their territory from which they obtain food, they do so by synthesizing antibiotics and other toxic metabolites. Fungi also require minerals like iron as haeme, sulfur from cysteine, nitrogen and phosphorus etc. Sabraud Dextrose Agar (SDA) is one of the most common Medias used in mycology. It was used formulated by Sabraud in the year 1892 for culturing dermatophytes. Brain Heart infusion agar is mostly used for culturing dimorphic fungi. Other Medias like BiGGY Agar is used mainly for identification of Candida spp. Birdseed Agar is a selective and differential media for isolation of Cryptococcus neoformans. Cryptococcus neoformans can utilize the caffeic acid as a substrate due to the presence of an enzyme, Phenoloxidase producing melanin. Cornmeal Agar is mostly used for inducing sporulation in Candida spp. Chloramphenicol and cyclohexamide are used in media for their antibacterial and antifungal actions respectively.

Disease caused by fungi

Diseases caused by fungi are called Mycosis. It can be categorized as superficial mycoses, subcutaneous mycoses and systemic mycoses. Fungi cause damage by tissue invasion (mycotic); toxin production (Mycotoxic) and induction of hypersensitivity.

Some of the factors that predispose to fungal diseases include immunosuppression, immunological defects, prolonged antibiotic therapy, metabolic and neoplastic diseases, immaturity, aging and malnutrition, exposure to heavy challenge of fungal spores, traumatized tissue, persistent moisture on skin surface etc.

Dermatophytes are fungi that grow on superficial layer of skin (skin, hair, claws) utilizing keratin. Dermatophytic infections are commonly referred to as ringworms. Dermatophytes affecting animals mostly belong to genera Microsporum and Trichophyton. Dermatophytes can be geophilic saprophytic, zoophilic or anthropophilic. Microsporum canis causes ringworm in cats, but it can also affect dogs and humans, hence it is considered to be of zoonotic significance. Ringworm in dogs is most commonly caused by Microsporum canis, but Microsporum gypseum and Trichophyton mentagrophytes can also be associated with canine dermatophytosis. Microsporum canis and Microsporum gypseum infections are usually acquired from soil. Trichophyton verrucosum causes ringworm in cattle whereas ringworm in horses is mostly caused by Trichophyton equinum and Trichophyton mentagrophytes. In pigs, Microsporum nanum is most commonly associated with dermatophytosis. Trichophyton mentagrophytes is usually found in rodents and some companion animals. It is also considered to be zoonotic.

Aspergillosis in animals is mostly caused by Aspergillus fumigatus (most common), Aspergillus flavus, Aspergillus niger, Aspergillus nidulans, Aspergillus terreus etc. A. flavus is most commonly associated with aflatoxicosis. In birds, Aspergillus mostly causes respiratory diseases like brooders pneumonia (mostly in the newly hatched chicks), air sac infections, and bronchopulmonary infections. Dissemination of infections to the brain is also seen, manifested by torticollis and disturbance in equilibrium. Yellow nodules are often seen in the respiratory organs or in the body cavities. In ruminants, it causes mycotic abortion, mycotic

pneumonia. In horses it causes gutturomycosis manifested by epistaxis and dysphagia, nasal granulomas, intestinal aspergillosis in foals. It causes otitis externa, chronic rhinitis in dogs

Candida albicans are commensals in the intestinal and genital tract (mucocutaneous areas) and are mostly responsible for localized mucocutaneous diseases. In birds, it causes 'Thrush' of mouth, oesophagus or crop (crop mycosis, sour crop). Candidiasis is often called as moniliasis. In cattle, it causes mastitis. Cryptococcus neoformans are yeasts found normally in the environment, in soil and pigeon droppings. Infection is acquired mainly due to inhalation of the spores or due to contamination of wound.[1] In dogs, it can cause nasal granulomas; central nervous system involvement and eye involvement causing blindness are also seen.[2] In cattle, it causes mastitis. In immunocompromised humans, it causes Cryptococcal meningitis and lung infections.

Histoplasmosis is usually caused by the inhaling the spores of Histoplasma capsulatum found in soil contaminated with the droppings of birds and bats.[3] It is manifested by lesions in the lungs and intestine of humans and companion animals. In equines, Histoplasma farciminosum causes Epizootic Lymphangitis. Coccidioidomycosis also known as Valley fever is caused by the fungus Coccidioides immitis. Humans and dogs mostly acquire the infection from soil. It is not contagious and hence cannot spread from one infected animal to another. It is considered as a major biohazard for the laboratory personnel. Sporothrix schenckii causes sporotrichosis in horses, companion animals and humans manifested mostly as skin or cutaneous lesions. It is mostly found in soil, plants, hay etc. It is contagious and also has significant zoonotic risk. Blastomyces dermatitidis causes North American Blastomycosis in dogs and humans.

Mycetoma is a chronic, progressive destructive morbid inflammatory disease affecting foot or other body parts. It occurs due to entry of the fungal organism through the penetrating wounds characterized by drainage of the 'grains' of fungal colonies from the wound.4It is caused by the fungus Cuvularia geniculata, Madurella mycetomatis, Pseudallescheria boydii etc.

Rhinosporidiosis caused by Rhinosporidium seeberi in humans, horses, cattle and dogs is a granulomatous disease affecting the mucous membrane of respiratory tract, conjunctiva and rectum.

An insight into Antifungal Therapy

Antifungal drugs are the drugs aimed to treat fungal infections by targeting various structural and functional components of the fungal organism essential for its survival like the cell wall, cell membrane, nucleic acid synthesis, growth and division etc. Antifungals that aim the fungal cell walls are called cell wall synthesis inhibitors. These act by inhibiting the b-(1, 3)-glucan synthase thus preventing the formation of b-(1, 3)-glucan in the cell wall leading to osmotic instability and death of the fungus. Hence, these are also known as the penicillin of antifungal drugs. Echinocandins like Caspofungin, Micafungin, and Anidulafungin etc comes under this category. Caspofungin is the first commercially available drug under this group obtained from a fungus, Glarea lozoyensis, used to treat Candidiasis and Aspergillosis. As cell wall is not a component of animal cells, these antifungals are more selective in action and less harmful to the host. Fugal cell membrane has ergosterol as prominent sterol rather than cholesterol. Antifungals target the fungal cell membrane in two ways. They can directly bind to ergosterol causing pore formation and leakage of ions resulting into internal acidification and death of fungus like the Polyene antibiotics. Amphotericin B, Nystatin, Natamycin are the Polyene antibiotics. AMB is the drug of choice for systemic mycoses caused by dimorphic fungi in immunocompromised animals. The other category of drugs acts by interfering with the ergosterol biosynthesis. Allylamines and Azoles are the drugs under this category. Allylamines act by inhibiting squalene epoxidase, preventing the conversion of squalene to ergosterol. Squalene alters the membrane permeability and results into fungal death. Allylamines like Terbinafine and Naftifine are mostly used to treat Dermatophytic infections. Azoles act by inhibition of 14alpha-demethylase which is a cyt 450 dependent enzyme and thus inhibit ergosterol synthesis, leading to disruption of fungal membrane and membrane bound enzymes, whereas cholesterol synthesis in mammals is not affected because it doesn't require 14alpha-demethylase. It also leads to inhibition of mitochondrial cytochrome oxidase leading to accumulation of peroxides that cause auto digestion of the fungus. Ketoconazole, Miconazole, Enilconazole, Clotrimazole, Fluconazol, Itraconazole, Voriconazole are some of the azoles available for use. It can be used to treat systemic mycotic infections. Some of the side effects of using Ketoconazole in man are gynecomastia, embryo

toxicity and teratogenicity. The third category of drugs is the nucleic acid synthesis inhibitors like Flucytosine. It is analogue of cytosine, so it enters the fungal cells via cytosine specific permease which is not found in mammalian cell. Flucytosine converts into active metabolite, 5-fluorouracil after entering the fungal cell. 5-fluorouracil acts as anti-metabolite by competing with uracil, ultimately interfering with the RNA and protein synthesis. It has narrow spectrum and fungistatic action. It can be used to treat Candida, C.neoformans infection. 5-FC treatment can cause bone marrow suppressions manifested by leukopenia, thrombocytopenia and/or pancytopenia. Hepatotoxicity, Nephrotoxicity, GI disturbances are also some of the side effects associated with the use of these antifungals.

The fourth type of antifungals is Griseofulvin. It acts by disorganizing the spindle microtubules. It also affects cytoplasmic microtubules. It is fungistatic in action and is used to treat dermatophytosis. Some of the locally acting antifungals are Iodine, Copper preparations, dyes like crystal violet, organic acids like benzoic and salicylic acids used in Whitefield's ointment (3% salicylic acid; 6% benzoic acid) etc. Some of the essential oils are also known to have some antifungal actions like Thyme, Lavender etc.

Conclusion

Fungal infections are generally very difficult to treat because, unlike bacteria, fungi are eukaryotes and antifungals that kill fungi also harm the eukaryotic host. Antibiotics only target prokaryotic cells, whereas compounds that kill fungi also harm the eukaryotic animal host. Fungal infections tend to be of chronic nature requiring prolonged treatment with antifungal drugs. Antifungal resistance and host-related adverse reactions further limit the development of antifungals against fungal pathogens. Moreover emergence of antifungal resistance among fungus has further complicated the challenge in developing antifungal drugs in the future.

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