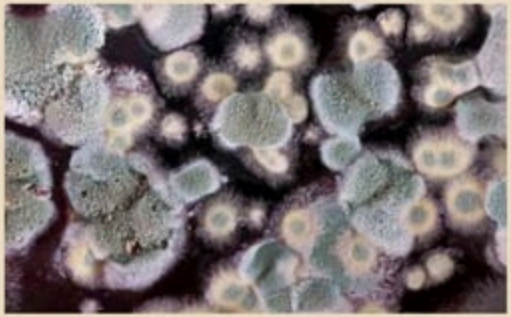
Immunity to fungal infection



Presented by:

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Introduction

- Fungi - diverse ubiquitous group of organisms
- Used in fermentation, penicillin production.
- Million of fungi known to exist. Only 400 potential agent.
- Infection may result from exogenous organisms due to injury or inhalation or from endogenous organisms such as commensals present in the gut and on the skin
- First human fungal disease –ring worm
- Most of them oppurtunistic –affects immune compromised person
- Fungal diseases are called mycoses classified based on

  1.site of infection

  2.route of infection

  3.virulence

Site of infection :

superficial
cutaneous
subcutaneous
deep or systemic

Route of infection:

endogenous
exogenous

Virulence:

primary –pathogenic organism
opportunistic –commensal organism

Predisposing factors

- Some time it may hypersensitivity and granuloma formation.
- Environmental factors also plays important role like:

1. Moisture of environment
2. Occupation
3. Metabolic status of the host
4. immune status of the animal

Predisposing factors

Fungal pathogen	Host factor
Candida (mucosal)	Impaired cell mediated immunity
Candida (disseminated)	Impaired mucosa or integument, neutropenia
Aspergillus	Neutropenia, high-dose corticosteroids
Cryptococcus	Impaired cell mediated immunity, corticosteroids
Zygomycetes	Neutropenia, deferoxamine treatment, corticosteroids, diabetic ketoacidosis
Fusarium	Neutropenia, impaired integument, corticosteroids
Scedosporium	Neutropenia
Trichosporon	Neutropenia, impaired integument

Barriers of innate immunity controls most fungal infection

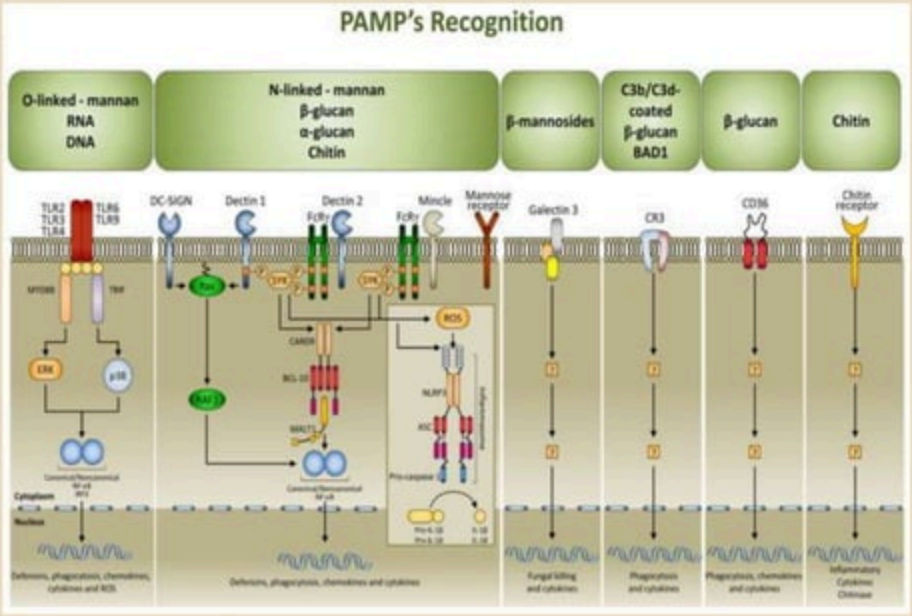
- If defence mechanism adequate –infection self limiting
- If not adequate chronic or sytemic or fatal infection occur

- Innate immunity

- Adaptive immunity
  1. Humoral- less
  2. cell mediated → Th_1 cell –IFN gamma-enhance immune response
     → Th_2 cell & T_{reg} cell-suppress immune response
- Cell mediated immunity is essential against deep sitted chronic fungal infection which is triggered by lymphcytes and its products lymphokine & monokines

Fungal PAMP

1. Beta glucans
2. Mannans
3. Chitin



PRR Receptor for fungus

- Dectin 1,2
- Toll like receptor 2,4,9
- Complement receptor -3

PAMP`S and PRR for differernt pathogen

Fungal species	Fungal PAMPs	Recognition of fungal PAMPs by PRRs and co-receptors	PRRs co-receptors with confirmed physical interactions
Candida albicans	GXM – glucuronoxyloman	TLR4	Galectin-3; Dectin-1; SIGNR1
	N-linked mannan	TLR4	
	O-linked mannan	TLR4	
	PLM – phospholipomannan	TLR2; TLR4	
	β-glucan	TLR2/Dectin-1	
	genomic DNA	TLR9	
	ssRNA	TLR7	
Aspergillus fumigatus	GXM – glucuronoxyloman	TLR4; TLR1/TLR2; TLR2/TLR6 (only in mice)	
	PLM – phospholipomannan	TLR2/TLR1; TLR2/TLR6	
	Undefined ligands on hyphae and conidia	TLR2	
	dsRNA	TLR3	
Histoplasma capsulatum	β-glucan	TLR2/ Dectin-1	Dectin-1
Coccidioides posadsii	β-glucan	TLR2/ Dectin-1	Dectin-1
Cryptococcus gattii	GXM - glucuronoxyloman	TLR2/TLR1; TLR2/TLR6	
Cryptococcus neoformans	GXM – glucuronoxyloman	TLR2/TLR1; TLR2/TLR6; TLR4	
	genomic DNA	TLR9	
	PLM – phospholipomannan	TLR2/TLR1; TLR2/TLR6	

Local defence mechanisms

- Local mucosal immunity is as important as systemic cell mediated immunity.
- Mucosal infection prevented by salivary proteins, such as lactoferrin, beta-defensins, histatins, lysozyme, transferrin, lactoperoxidase, mucins, and secretory immunoglobulin A.
- Impair adhesion and growth of Candida in the oropharyngeal cavity.

Innate immunity

- Skin epithelium - pH, lysozyme,sebum
- GI tract-acidic , enzymes,
- RT-inhaled spores trapped in mucosa & coughed out ,
- Surfactant proteins in lungs. sp-A, sp-D prevents pulmonary infection
- Urinary tract –urine out flow & sloughing of epithelial cells

- Commensal organism-lactobacilli, bifidobacteria –candidiasis
- Long term antibiotic therapy destructs commensals predisposes to oral and genital candidiasis
- Defensins –cysteine rich proteins secreted by host cells

Innate immunity

- Phagocytosis by neutrophil & macrophage –yeast form easy than hyhae form
- Neutrophil-Reactive O2 species ,lysozomal enzymes
- Natural killer cell-cytolytic enzmes,IFN-Y ,stimulates macrophage to kill pathogen

Complement system

- Resting conidia are potent activators of alternative complement cascade and neutrophils chemotaxis
- Germinating conidia and fungal hyphae – classical pathway of complement activation
- Alternative and lectin pathways triggered by fungal cell wall components

Complement system

- Mannose binding proteins recognize fungi and activate complement cascade
- Complement components bind to the organism and cause phagocytosis and intracellular destruction by MAC
- Complement receptors CR1, CR3 and CR4 bind fungal proteins and mediate phagocytosis

Immune cells & receptor for fungus

- Collectins-increase permeability of fungal cell wall

- TLR-germ line coded:
  expressed in macrophage, B cell ,T cell, endothelial cell
  – TLR2 (IL-10) and TLR4 (IL-1α and IL-1β) are stimulated by fungal spores & elicits the immune response

- Protease activated receptor: protease released in inflammation from fungus or host ,activates PARs
- Soluble receptor:
  pentraxin 3-collectin family –it is soluble opsonic receptor

Neutrophil

- Express TCR & dectin1

first cell to be recruited , in turn recruits other cells

-limit growth by oxidative & non oxidative mechanism

- O2 dependent mechanism-No2, reactive O2 intermediate ,peroxy nitrite

ROI –nucleic acid break, lipid peroxidation ,

- Oxygen independent :

  degranulates , release of cationic peptides ,lysozyme, defensins ,cytokine,chemokine

- Essential host defense –candida, aspergillus, fusarium
- Cancer therapy –neutropenia –susceptible to aspergillosis & candidiasis

Dentritic cell

- Dendritic cells have an instrumental role in linking innate and adaptive responses to a range of pathogenic fungi including Aspergillus fumigatus, Cryptococcus neoformans and C. albicans.
- Dendritic cells that ingest the yeast form induce differentiation of CD4+ T cells toward a Th1 pathway while hyphae induce Th2 responses.
- In dendritic cells FcγRII and mannose receptors are essential for fungal uptake and antigen presentation to T cells

Dendritic cells

- Langerhan cells, immature dermal dendritic cells –first line of defence
- Express C type lectins langerins receptor that binds fungus
- Immature dentritic cell ingest the fungal pathogen releases cytokine, kills by respiratory burst

Capture and process antigens, express both MHC-II molecules as well as lymphocyte co-stimulatory molecules, migrate to lymphoid organs and secrete cytokines to initiate aquired immune responses

Macrophage

- phagocytosis ,destruction of fungi
- opsonize fungus by Ab, complement or collectin
- Functions as APC, presents fungal peptide to CD4 ,CD8 cell.
- Alveolar macrophage –first line of defence against respiratory infection ex:A.fumigatus
- Involved in granuloma –destructs fungus
- Macrophage –cyptococcus pneumocysti
- Neutrophil- C. albicans , A.fumigatus
- The phagocytes are very important in defence against Candia, Aspergillus and Zygomycetes as is evidenced by their severity in granulomatous diseases,myeloperoxidase deficiency and cytotoxic chemotherapy.

Humoral immunity

- Even though antibodies are produced against many fungi, their role in protection is not very clear.
- However,antibodies help in clearing fungal pathogens through opsonisation, which is important against Candida and Cryptococcus.
- Another component of humoral immunity is the complement, which can act as opsonins and may even cause damage to their cells through complement activation.
- Antibodies are important to fungal serodiagnosis.

Hypersensitivity

- As a result of dermatophyte infection some fungus-free skin lesions of variable morphology occur elsewhere on the body, which are thought to result from hypersensitivity to the fungus.
- These reactions are called "id reaction".
- These reactions are also seen in Candida infections. An inflamed boggy lesion of the scalp called the kerion may result from a strong immune reaction to the dermatophyte.
- Granulomas due to intracellular fungi represent delayed hypersensivities.

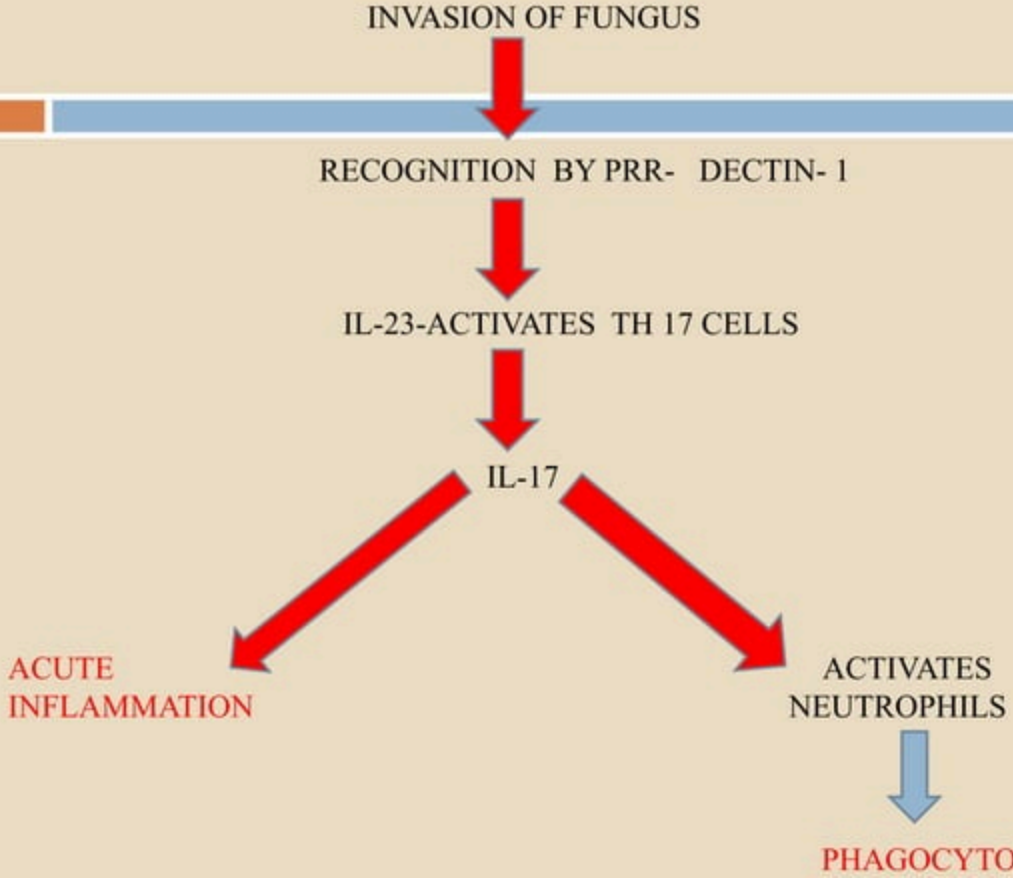
Hypersensitivity

- Many fungi are significant allergens to humans, the allergens being spores, conidia, hyphae and other fungal products.

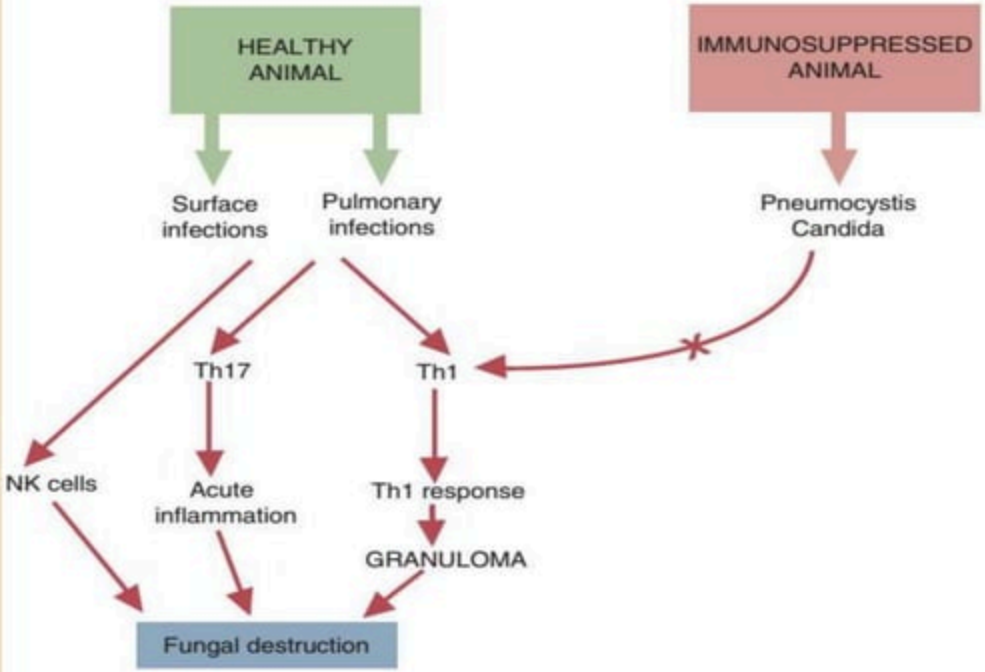
- On inhalation they may produce allergic pulmonary diseases such as allergic bronchopulmonary aspergillosis, farmer's lung, maple bark stripper's lung, bronchial asthma etc, which may be Type I or III hypersensitivity.

Expression of T-cell-mediated immunity to fungi includes:

1.delayed-type hypersensitivity
2.contact allergy
3.chronic granulomatous reactions


INVASION OF FUNGUS
RECOGNITION BY PRR- DECTIN- 1
IL-23-ACTIVATES TH 17 CELLS
IL-17
ACUTE INFLAMMATION
ACTIVATES NEUTROPHILS
PHAGOCYTOSIS

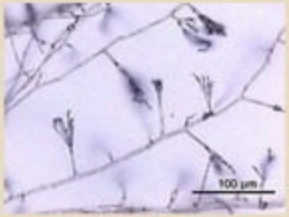
Cell mediated immunity- major immune response



Fungal evasion

- *Candida albicans* –binds TLR2-release IL10-generation of T reg cell & Th2 cell

- *A. fumigatus* –transform to hyphae –loss of TLR4 recognition but TLR 2 intact cause release of IL 10



Fungal hyhae

Fungal vaccines

- Insol Dermatophyton

  T. equinum

  Inactivated conidia & mycelium

  Prophylactic & therapeutic

- Feo-o-vax-mc-k (fort dodge)

  Inactivated mycelium of M.canis

- Ringvac bovis LTF-130

  Ring worm-Bovine

  LTF-130 strain of *T. verucosum* –Live vaccine

THANK YOU