

Topic 5: General Aspects of Fungal Immunology and Pathology

Natural Immunity (Innate Immunity/Nonspecific Immunity)

Natural immunity to fungi is high.

Natural immunity involves innate defenses:*

- a) physical barriers, such as skin & mucus membranes
- b) chemical barriers, such as secretions, serum factors
- c) natural effector (sentinel) cells (e.g. dendritic cells, neutrophils, luminal macrophages, etc.), which may be phagocytic or nonphagocytic

*may destroy pathogen, or at least limit infection until adaptive system develops

Factors that Affect Host-Fungus Interactions

- c) Those that allow fungus to enter host and cause disease*
- d) Those of the host that either limit the growth or the survival of the fungus in tissue**

*virulence factors

**host factors

Relationship of Natural Immunity^o to Outcome of Mycoses

1. Infection often depends on the a) exposure to a sufficient inoculum size, particularly as it relates to pulmonary inoculum, or b) to traumatic implantation of the inoculum directly into tissue.

-----> primary infections

- a) systemics "true"
- b) subcutaneous

2. The general resistance of the host. The lower the resistance the more severe the possible outcome.
3. The inherent virulence of the fungus

Thus for primary (1^o) pulmonary ("true", endemic) pathogenic fungal (systemic) infections, e.g.:

Histoplasmosis*+

Blastomycosis*

Paracoccidioidomycosis*

Coccidioidomycosis*+

(1^o)

Infection

- 1) is usually associated with an endemic area &/or infested hazard site, and
- 2) with the inhalation of some particular number of infecting propagules (spores).**

number vs resistance vs virulence

^o relatively high for fungi

*considered to be of relatively high virulence

+recovery ---> induces protective resistance (specific immunity)

****normal patient = asymptomatic, resolving or chronic
compromised patient = progressive and systemic**

Opportunistic Systemic Infections (2^o)

e.g.: Aspergillosis*
Candidiasis*
Zygomycosis*
Cryptococcosis*?

Generally the fungi of these mycoses are thought to be less virulent than those of the 1^o endemic mycoses. Mycoses generally depends on lowered host resistance

Low doses of inoculum and low resistance →
disease e.g., systemic Aspergillosis

High doses and normal resistance may or may not →
disease e.g., Farmers' Lung (colonizing &/or chronic pulmonary aspergillosis) (Pigeon Breeders' Disease, chronic pulmonary cryptococcosis) etc.

* Recovery → no specific immunity (specific induced
resistance)
. . Host defenses are important for resistance to fungal infections

Natural Effector Cells and the Professional Phagocytes The First Line of Defense

1. Granulocytes (Polymorphonuclear Leucocytes - PMNs)

Three types - neutrophil, eosinophil & basophil. All have lobed nuclei, granules in cytoplasm, but only neutrophils are phagocytic.

Neutrophils circulate in blood & tissues and are the first phagocytes to arrive at the site of inflammation (low #s of neutrophils = neutropenia; contributes to aspergillosis, candidiasis, etc.)

2. The Mononuclear Phagocytes

The monocytes - a mononuclear leukocyte that circulates briefly in the blood stream

The macrophages* - a mononuclear leukocyte that has left the bloodstream to migrate in tissue

They are the second type of phagocyte to arrive at the site of inflammation

*they a) also are antigen presenting cells (APCs), b) release cytokines that stimulate specific immune responses, c) are part of RE system, d) are less efficient killers than neutrophils except when activated, and e) are the home of intracellular pathogens (e.g. *H. capsulatum*, *P. marneffei*)

3. Dendritic cells

An APC gatekeeper that acts between the innate and adaptive immune responses; found in small numbers in all surface epithelia and most other solid tissues, and as a rare cell in blood and lymph.

Importance of CMI (T_H1 Immune Responses)

Temporal relationship between disease susceptibility and severity, and depressed T- (thymus) derived lymphocytic function* suggests that cell mediated immunity (CMI) is more important in specific host resistance to fungi.

***vs B-(bone marrow) derived lymphocytic function and antibody production (T_H2 immune responses). However, antibodies are important to fungal serodiagnosis, and the complement cascade.**

Evidence for role of CMI Defenses in Fungal Pathogenicity

1. **Fungi have enhanced pathogenicity in immunosuppressed humans or in T-cell-deficient experimental animals.**
2. **Specific fungal antigens have been demonstrated to induce blastogenic transformation and release of lymphokines among sensitized lymphocytes.**

***These lymphokines are presumed, or have been demonstrated, to function by interacting with portions of the CMI system; lymphokines are cytokines produced by lymphocytes vs monokines produced by monocytes and m ϕ .**

Lymphokine interactions function to:

- a) **localize and activate macrophages and include**
 - i. **m ϕ migration inhibition factor;**
 - ii. **macrophage activating factor**
 - b) **act directly on lymphocytes as do**
 - i. **blastogenic factor;**
 - ii. **lymphocyte chemotactic factor;**
- or
- c) **mediate killing or inactivation of target cells via lymphotoxin(s).**

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

1. **delayed-type hypersensitivity (DTH)**
2. **contact allergy**
3. **activation of M Φ & cytotoxic T cells**
4. **chronic granulomatous reactions***

*** predominant tissue reaction to fungi in CMI-competent patient; the DTH reaction the body mounts against a pathogen that it cannot kill; the DTH reaction in which large numbers of M Φ (epitheloid cells in this case, some of which may fuse to form multinucleated giant cells that may be more effective phagocytes) congregate together with lymphocytes and fibroblasts around large or numerous target fungi.**

How to confirm CMI functioning in patient with mycosis*

1. **Skin testing assays for delayed-type hypersensitivity (traditional)**
2. **Lymphocyte transformation assays (LT assays)**
3. **Macrophage migration inhibition factor assays (MIF assays)**
4. **Cytotoxicity assays**

Traditionally #1 was most important. #2, 3 and 4 wave of today and tomorrow

***Sometimes useful also in diagnosis, with symptoms, culture &/or serology**

I. Skin Test Reactions

- eg. allergy
1. Wheal/flare Response possibly to IgE antibodies and exhibited within ~ 10 - 30 min.
 2. Arthus Reaction = ~ 2 - 4 h to 10 - 24 h; IgE-mediated.
- eg. broncho-pulmonary aspergillosis
- A. mediated by precipitable antibodies which fix complement, aggregate and excite polymorphonuclear leucocyte infiltration
 - b. is accompanied by severe, localized immediate-type hypersensitivity
- Histo/Cocci exposure/ . Immunity
3. Delayed Type Hypersensitivity (DTH) read⁺ as mm induration* w or w/o erythema** at 24 - /48 H***

* hardening and **reddening; ⁺5mm = +positive reaction
energy may → poor prognosis. Cocci, Histo, *Candida* + to - → loss of immunocompetency
***depends on antigen-sensitized T lymphocytes

II. LT Assays (Lymphocyte Transformation)

Involve sensitized T lymphocyte responses to specific fungal antigens as measured by increased synthesis of DNA, RNA or protein or measured by > # of cells (microscopic measure) of the blast type resulting from blast cell transformation.

- Can use:
1. peripheral blood
 2. spleen tissue
 3. lymph node tissue
 4. other tissue which contains sufficient lymphocytes

III. Macrophage Migration Inhibition Factor Assays (MIF)

Involves sensitized lymphocytes that respond to specific antigens in vitro by production of MIF.

MIF lymphokine acts to retard or inhibit migration of macrophage

MIF production correlates well with skin test data

IV. Cytotoxicity Assays

Involve activated lymphocytes that release cytotoxins, which bring about lysis of target cells.

Measure:

- 1) isotope uptake by cells remaining after killing
- 2) release of radioactivity (^{51}Cr) from prelabeled cells
- 3) microscopic counts of living vs dead cells

All generalizations dealing with fungal immunology and pathology must be tempered by consideration of:

1. The fungus involved; e.g. those with
 - a) low virulence
 - b) high virulence
1. The exact immunological state of the host
2. The number of infecting units involved
3. The route of infection
4. The site of the lesions involved
5. The duration of the infection

Data indicate, at least with a cryptococcal system, that granuloma formation is a two stage CMI process:

1. phagocytosis by $\text{M}\phi \rightarrow$ pyogenic (or cystic) type reaction
2. followed by another CMI step that promotes granuloma formation and possibly more killing

General Pathology

For Primary Endemic Systemic Mycoses & Many Subcutaneous Mycoses

- 1) pyogenic reaction*
- 2) followed by a granulomatous reaction**
usually 1^o in immunocompetent patient

For Opportunistic Systemic Mycoses & Some Subcutaneous Mycoses

- 1) necrotic → extensive tissue death
- 2) suppurative*** lesions
usually 2^o in abrogated patients

*pusy/pus producing/sometimes cystic → fluid-filled membranous sac

tumor-like formation usually of lymphoid** and epithelioid cells that are slow growing and therefore produce chronic granulomatous tissue around living fungus

***draining fluids

****often with multinucleated giant cells

Granuloma Development

Data indicate, at least with a cryptococcal system, that granuloma formation is a two stage CMI process:

1. phagocytosis by MΦ → pyogenic (or cystic) type reaction
2. followed by another CMI step that promotes granuloma formation and possibly more killing

Superficial Mycoses*

1. generally do not elicit host cellular response
2. generally → no tissue damage
3. often do little to make host aware of presence

*in normal hosts

Cutaneous Mycoses

1. **The dermatophytoses or the ringworms**
 - a) caused by known or suspected **Plectomycetes** that → eczema, then allergic and inflammatory skin reaction
 - b) all agents are included in the form-genera *Microsporum*, *Trichophyton*, *Epidermophyton*
2. **Dermatomycosis** - caused by non-dermatophytes other than *Candida sp.*
3. **Cutaneous candidiasis** - skin and mucocutaneous tissue infections by *Candida sp.*

Subcutaneous Mycoses

1. **Large heterogenous group of diseases of normal hosts**
2. **Tend to localize in subcutaneous tissue***
3. **Tend to be chronic***
4. **Tend to be initiated by traumatic implantation of fungi with relatively low virulence**
5. **Can be very serious in compromised hosts**

***in normal hosts**

Systemic Mycoses

Primary Endemic Mycoses (see Handout 1)

Secondary Opportunistic Mycoses (see Handout 1)