Immunological Aspects of Infectious Disease (Fungi & Parasite)

Dr. dr. Loeiki Enggar Fitri MKes. SpParK
1. Introduction
2. Component of the immune system
3. Non specific immunity to bacteria, virus, fungi & parasite
4. Specific immunity to bacteria, virus, fungi & parasite
5. Immune evasion of Fungi
6. Immune evasion of parasite
Introduction

- The mechanism underlying specific immunity to many micro-organisms remain unknown
- While the immune response has evolved to confer protection against invading antigens → human pathology arises
Introduction

- Protective immunity to particular tropical parasitic infection is frequently inadequate/non-existent → prospect to vaccination
- People afflicted with tropical infections often suffer a general immunodeficiency
- Immune responses to tropical infections → help in diagnosis and management
### Immunopathological consequences of tropical infections

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<th>Mechanism involved</th>
<th>Examples</th>
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<td>Type I (allergic)</td>
<td>IgE</td>
<td>Lung ascariasis</td>
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<td>Type II (antibody-mediated)</td>
<td>IgG, Autoantibody</td>
<td>Malaria anaemia, Streptococci (RHD)</td>
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<td>Type III (immune complex)</td>
<td>immune complexes</td>
<td>Malaria kidney</td>
</tr>
<tr>
<td>Type IV (cell-mediated)</td>
<td>Macrophages</td>
<td>Tuberculoid Leprosy</td>
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Kuliah FK - Imunologi Parasit
Component of the immune system

The non specific immune system:
- External barriers (skin, mucosal surfaces, flushing mechanism, normal microbial flora)
- Innate immune system (phagocyte cells, soluble factors & complement)

The specific immune system/acquired immune response:
- Humoral immune response
- Cell-mediated immune response
Non specific immunity to bacteria, virus, fungi & parasite

- The skin is the most important barrier to invading microorganism:
  a. secretes sebum → inhibits growth of microorganism.
  b. Normal microflora → compete with pathogenic organisms
- A & b → colonization inhibition
3. Non specific immunity to bacteria, virus, fungi & parasite

- Mucosal surfaces mechanism:
  a. Ciliary movement
  b. Surface phagocyte
  c. Enzyme & surface antibody (secretory IgA)
  d. Mechanical washing by tears or urine
  e. Obligate aerobes produce potent inhibitors of bacterial growth (Bactericins)
  f. Obligate anaerobes produce free fatty acids

→ Environment less supportive to microorganism
Non specific immunity to bacteria, virus, fungi & parasite

Pathogen

PHAGOCYTIC CELL

Phagosome

Lysosome containing enzymes

1. Chemotaxis
2. Adherence through PAMP recognition
3. Membrane activation through 'danger' signal
4. Initiation of phagocytosis
5. Phagosome formation
6. Fusion
7. Killing and digestion
8. Release of degradation products
Cellular Innate Defenses

- Pathogens entering the mammalian body are subject to phagocytosis.
- Phagocytic cells recognize groups of pathogens by TLRs, Toll-like receptors.
Non specific immunity to bacteria, virus, fungi & parasite
Evasion of killing phagocytic cells by microorganism

Chronic Infection
Re-activation
Carrier state
Co-factor for development of certain malignancy
Overview of the Specific Immune Response

**Humoral (Antibody-Mediated) Immune Response**
- Antigen (1st exposure)
  - Engulfed by Macrophage
  - Becomes Antigen-presenting cell
  - Stimulates Helper T cell
  - Stimulates B cell
    - Gives rise to Plasma cells
      - Secret Antibodies
        - Defend against extracellular pathogens by binding to antigens and making them easier targets for phagocytes and complement.

**Cell-Mediated Immune Response**
- Antigens displayed by infected cells activate Cytotoxic T cell
  - Stimulates Memory helper T cell
    - Stimulates Memory B cells
    - Stimulates Memory T cells
      - Gives rise to Active cytotoxic T cells
        - Defend against intracellular pathogens and cancer by binding to and lysing the infected cells or cancer cells.
Central Role of Helper T Cells

Interleukin-2 and other cytokines activate $T_H$ cells, $B$ cells, and $T_C$ cells.

Humoral immunity (secretion of antibodies by plasma cells)

Cell-mediated immunity (attack on infected cells)
Specific immunity to bacteria, virus, fungi & parasite

- Extracellular Ag \(\rightarrow\) induce humoral immune response
- Intracellular Ag \(\rightarrow\) induce cellular immune response

The Ags that are capable to bind on specific surface immunoglobulin of B lymphocyte and induce antibody production are referred to as T-cell-independent Ags (figure)
Specific immunity to bacteria, virus & parasite
Specific immunity to Intacellular bacteria, virus & parasite

Fig. 1. Schematic diagram illustrating the interplay between Th1- and Th2-cell-regulated mechanisms of immunity to asexual erythrocytic stage *Plasmodium chabaudi* *chabaudi* AS infection in mice. Full arrows represent positive regulation; broken arrows represent negative regulation.
Cytotoxic T Cells Lyse Infected Cells

1. **T_c** cell binds to infected cell.
2. Perforin makes pores in infected cell’s membrane.
3. Ions and water enter the cell via pores.
4. Infected cell lyses.

**Diagram Notes:**
- Class I MHC
- CD8
- Antigen fragment
- T-cell receptor
- Perforin
- Pore

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Mycoses: diseases caused by fungi

- Asthma and allergy
- Skin disease
  - cutaneous
  - subcutaneous
- Recurrent vulvovaginal candidiasis
- Inflamatory Bowel Disease
- Invasive Fungal Disease
Superficial Mycoses

- **Tinea (Pityriasis) versicolor** -- pigmented lesions on torso
- **Tinea nigra** -- gray to black macular lesions often on palms
- **Black piedra** -- dark gritty deposits on hair
- **White piedra** -- soft whitish granules along hair shaft
- **Often associated with organisms** of the genus *Malassezia*
- **All are diagnosed by microscopy** and are easily treated by topical preparations.

<table>
<thead>
<tr>
<th>Clinical Name</th>
<th>Site</th>
<th>Most frequent organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinea capitis (epidemic)</td>
<td>scalp</td>
<td>Trichophyton tonsorus, Microsporum audouinii</td>
</tr>
<tr>
<td>Tinea capitis (non-epidemic)</td>
<td>scalp</td>
<td>Microsporidium canis, Trichophyton verrucosum</td>
</tr>
<tr>
<td>Tinea favosa</td>
<td>scalp, torso</td>
<td>Trichophyton sp.</td>
</tr>
<tr>
<td>Tinea barbae</td>
<td>beard</td>
<td>Trichophyton rubrum, T. verrucosum</td>
</tr>
<tr>
<td>Tinea coporis</td>
<td>torso</td>
<td>T. rubrum, M. canis, T. mentagrophytes</td>
</tr>
<tr>
<td>Tinea cruris</td>
<td>crotch</td>
<td>T. rubrum, T. mentagrophytes, Epidermophyton floccosum</td>
</tr>
<tr>
<td>Tinea pedis, manus</td>
<td>feet, hands</td>
<td>T. rubrum, T. mentagrophytes</td>
</tr>
<tr>
<td>Tinea unguium</td>
<td>nails</td>
<td>T. rubrum, T. mentagrophytes, E. floccosum</td>
</tr>
<tr>
<td>Tinea imbricata</td>
<td>torso</td>
<td>T. concentricum</td>
</tr>
</tbody>
</table>
Systemic fungal disease is most often associated with four organisms:

1. *Coccidioides immitis*
2. *Histoplasma capsulatum*
3. *Blastomyces dermatitidis*
4. *Paracoccidioides brasiliensis* (S. America)
Immune Response to Fungal Infection

Epithelial cells recognize pathogen associated molecular patterns (PAMPs) such as glucans, mannans and chitin.

In response they secrete cytokines and chemokines to attract PMNs which provide a first line of defense.

Natural immunity is high; physiologic barriers include Tissue temperature--fungi grow better at less than 37°C and Secretion of antimicrobial peptides
Activated neutrophils are critical in the defense against disseminated candidiasis and aspergillosis.
Specific Immune Response to Fungal Infection

The uptake of fungi by DCs promotes differentiation of T-helper cells.

A dominant T_{H1} response correlates with protective immunity to fungal infections.

Cell-mediated immunity predominates in protection against cryptococcosis, histoplasmosis and mucosal *C. albicans* infection.
Virulence factors help pathogenic fungi to evade host response and subvert basic immune processes.

Evasion of the immune response: yeast to hyphal transition; changing of surface glycoproteins; hydrophobins; survival in macrophage.
Systemic fungal disease
**Coccidioidomycosis**

A. **Immune Response:** T-cell mediated (Th-1):
   IL-2, IFN-γ

B. **Evasion of Defenses:** Resistant to killing by phagocytes
   -- protein rich, hydrophobic outer wall
   -- alkaline halo associated with urease

E. **Damage:** secreted proteinases break down collagen, elastin, hemoglobin, IgG & IgA
Histoplasmosis
(also called cave disease)

Caused by the dimorphic fungus *Histoplasma capsulatum*

Histoplasmosis is characterized by intracellular growth of the pathogen in macrophages and a granulomatous reaction in tissue.

These granulomatous foci may reactivate and cause dissemination of fungi to other tissues.
Histoplasmosis

**Immune Response**
1. Cell-mediated responses are of primary importance
2. Phagocytic activity of macrophage is considered an important component of resistance to drugs.
3. Activated macrophage can kill yeast cells

**Evasion of Defenses**
1. Survival in macrophages—elevates pH of phagosomes
2. Yeast cells absorb iron and calcium from host
3. Alteration of cell surface
**Blastomyces dermatitidis**

- **Evasion of Defenses**: Escapes phagocytosis by neutrophils and monocytes by shedding its surface antigen after infection.
- Alveolar macrophage provide a first line of defense.
- T-cell stimulated PMNs kill *Blastomyces* cells (by oxidative mechanisms).
- Conidia are more sensitive to killing by PMNs because yeast are too big.
- TH-1 response of primary importance.
Opportunistic Mycoses

**Cryptococcus neoformans**

About 30% of cryptococcus infections occur in patients with lymphoma (CNS). Major opportunistic infection in patients with AIDS

- **Evasion of defenses**: Yeast cells are resistant to phagocytosis because of capsule. Melanin protects against oxidative injury

- **Immune response**: Activated neutrophils have an increased capacity to phagocytize *C. neoformans*. Cell mediated immunity is a primary defense.
**Candidiasis**

**Immune Response**

- Hyphae are too big for phagocytosis but are damaged by PMNs and by extracellular mechanisms (myeloperoxidase and β-glucuronidase). Cytokine activated lymphocytes can inhibit growth of *C. albicans*.

- Resistance to invasive infection by Candida is mediated by phagocytes, complement and antibody, and T cell mediated immunity plays a major role. Patients with defects in phagocytosis function and myeloperoxidase deficiency are at risk for disseminated (even fatal) *Candidiasis*.

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Immunity to Parasite
Humoral immunity (Antibody) to parasite

- IgG → Malaria
- IgM → Malaria, Trypanosoma
- IgE → Extraluminal helminth
- IgA → Intra Lumenal helminth

a. Lysis by Antibody/complement

- Lysis sporozoite or merozoite of Plasmodium,
- Lysis Trypanosoma
- Lysis extraluminal helminth
b. Neutralized by antibody (parasite can no longer gain entry into the cells) using neutralising antibody to sporozoite or merozoite of Plasmodium, *Trypanosoma cruzi* & *Toxoplasma gondii*.

c. **Opsonization of Macrophages**
Plasmodium dan Trypanosoma.

d. **Antibody dependent cell mediated cytotoxicity (ADCC)**
Schistosoma, Trichinella & Filaria.
<table>
<thead>
<tr>
<th>Parasit</th>
<th>Sporozoit plasmodium, Cacing intestinal, Tripanosoma</th>
<th>Sporozoit plasmodium, merozoit T. cruzi, Toxoplasma gondii</th>
<th>Tripanosom Plasmodium</th>
<th>Schistosom T. spiralis Filaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mekanisme</td>
<td><img src="image1.png" alt="Diagram 1" /></td>
<td><img src="image2.png" alt="Diagram 2" /></td>
<td><img src="image3.png" alt="Diagram 3" /></td>
<td><img src="image4.png" alt="Diagram 4" /></td>
</tr>
<tr>
<td>Efek</td>
<td>Kerusakan langsung atau lisis oleh komplementen</td>
<td>Mencegah penyebaran melalui neutralisasi tempat ikatan, mencegah terlepas dari vakuol lisosom, mencegah inhibisi fuel lisosom</td>
<td>Meningkatkan efek fagositosis</td>
<td>ADCC</td>
</tr>
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</table>

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ADCC
Destruction of Large Parasites by ADCC
Granuloma formation

Granuloma form as a consequence of the body’s defence mechanism for walling off pathogens.

Granuloma can be defined as a focal, compact collection of inflammatory cells in which mononuclears predominate and are usually formed as a result of undegradable or persisting microorganism and are due to Delayed Type Hypersensitivity (DTH).

Granuloma is an active site of numerous enzymes and cytokines.
Intraluminal helminth:

- Most helminth extracellular & too large for phagocytosis. Some gastrointestinal host develops inflammation and hypersensitivity to expel the worms.
- The expulsion of some intestinal nematoda occurs spontaneously a few weeks after primary infection.
- There seem to be two stages in the expulsion which is achieved by a combination of T-dependent and T-independent mechanism.
Mekanisme Penghindaran Parasit dari Pengawasan Sistem Imun

a. Ukuran parasit yang besar
   Sulit untuk sistem imun mengeliminasi parasit dengan ukuran besar. Respon imun pertama adalah inflamsi untuk inisiasi ekspulsi, tetapi kebanyakan cacing tetap tidak bisa dikeluarkan.

b. Keragaman antigenik
   Parasit → beberapa stadium → tiap stadium cocok dengan Ab tertentu
   mis: Plasmodium → IgG penderita daerah endemis → efek terapeutik
- **African Trypanosomes** mempunyai suatu glikoprotein menutup permukaan tubuh. Protein yang bersifat imunodominan ini disebut *variant surface glycoproteins* (VSG)

- Gen yang mengkode protein ini adalah suatu “gene cassettes” yang menyebabkan VSG dapat *switch* secara reguler menjadi VSG dengan tipe yang berbeda.

- Ab. VSG tertentu tidak dapat digunakan untuk VSG tipe lain → parasit tak dikenal oleh hospes.
c. Belajar hidup dalam Makrofag
untuk Parasit Intrasel, mis: Toxoplasma, Trypanosoma, Leishmania

Cara:
- Menggagalkan fusi Lisosom & fagosom
  mis: Toxoplasma (≈ M. Tuberculosis)
- Menghindar dari Lisosom → cytoplasma
  mis: Trypanosoma
- Menyelimuti diri atau membentuk kapsul pelindung
  → tahan thd pengaruh lisosom
  mis: Leishmania (≈ M. Tuberculosa, M Lepra)
d. Supresi tanggap kebal
Parasit merusak sel dan jaringan limfoid, dengan cara:
1. Mengeluarkan bahan sitotoksik:
   - merusak jar. Limfoid
   - memecah molekul IgG
2. Melepaskan antigen dalam jumlah besar → mengganggu respon imun, dengan:

- Mengikat Ab → tdk mencapai parasit
- Memblok sel efektor
  → langsung (Tc)
  → Membentuk kompleks immun (sel K/ADCC)
- Menginduksi toleransi sel B dan T thd parasit
- Aktivasi Poliklonal → pelepasan bahan bahan mitogenik → Ab >> non spesifik
- Aktivasi sel supresor
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e. Subversi tanggap kebal, merubah sifat salah satu komponen sistem imun
Contoh: Cestoda \(\rightarrow\) Proteoglycan \(\rightarrow\)
\[\text{Inaktivasi komplemen}\]

f. *Anti-immune mechanism*
Leishmania memproduksi anti-oxidases untuk menetralisir produksi radikal bebas dari macrophag yang teraktivasi
g. Penyamaran antigenik
Parasit menggunakan Ag inang → mantel
mis: Schistosoma
- Schistosoma mengambil protein darah inang, seperti blood group antigens & molekul MHC class I & II, akibatnya, cacing bersifat "self".

Evasion strategies of ectoparasites of vertebrates.

Ectoparasites juga mempunyai strategi untuk menghindari pertahanan inang tapi bukan suatu immun evasion.

- Rapid feeding of blood-sucking insects to avoid host defensive movements.
- Use of 'hooks/claws' e.g. claws on tarsi of head lice etc. used to hold on to hair - allows parasite to survive grooming activities of host.
Terima kasih