Immunological Aspects of Parasitic Diseases in Immunocompromised Individuals

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Defense mechanism in human

(A)

Inflammatory

Autoimmunity
Acute bacterial infections

Allergies
Fibrosis

Chronic

Intracellular

Th17 (?)

Th1

Th1

Chronic protozoan & mycobacterial infections

Helminth infections ("modified type 2 profile")

Regulatory

Treg

Extracellular

Acute

Type 1

Type 2
Mechanisms of immune modulation

• Intracellular / extracellular parasites

• Dendritic Cells (DC) in peripheral tissues (as sentinel cells)

• Lymph nodes

• Naïve T cells

• Polarization of T cell development towards Th1, Th2 or T reg phenotype.
Acquired immunodeficiencies

• Deficiencies of the immune system often develop because of abnormalities that are not genetic.

• Two main types of pathogenic mechanisms:
  – Immunosuppression may occur as a biologic complication of another disease process.
  – Iatrogenic immunodeficiencies may develop as complications of therapy for other diseases.
HIV Infection

CD4 T cells is a viral receptor → "Death CD4 cells toll" within few days.

Several mechanisms:
- Direct killing as a result of the viral infection.
- Increasing susceptibility of infected cells to apoptosis.
- Killing by cytotoxic CD8 T cells

• HIV Infection
  →
  • Dysfunction of the immune system
    →
    Inducing opportunistic infection
Iatrogenic immunodeficiencies

- Due to some drugs either for the treatment of inflammatory diseases or to prevent rejection of tissues allografts e.g. corticosteroids
## ACTIVITY

<table>
<thead>
<tr>
<th>ACTIVITY</th>
<th>EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1, TNF-α, GM-CSF, IL-3, IL-4, IL-5, IL-8</td>
<td>Inflammation caused by cytokines</td>
</tr>
<tr>
<td>NOS</td>
<td>NO</td>
</tr>
<tr>
<td>Phospholipase A2, Cyclo-oxygenase type 2</td>
<td>Prostaglandins, Leukotrienes</td>
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<tr>
<td>Adhesion molecules</td>
<td>Reduced emigration of leukocytes from vessels</td>
</tr>
<tr>
<td>Induction of endonucleases</td>
<td>Induction of <strong>apoptosis</strong> in lymphocytes &amp; eosinophils</td>
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Human T lymphototropic virus type 1 (HTLV-1)

- HTLV-1 infected patients have a virally induced Th1 bias to their immune system (produce more basal IFN-γ, less polyclonal and parasite-specific IgE) → increased prevalence of SS infection, greater refractoriness conventional th, hyperinfection syndrome

- Coinfection with SS: ↑ population of HTLV-1 infected CD4+ CD25+ T cells and higher levels of circulating proviral DNA → accelerate disease course of HTLV-1 infection
Strongyloides stercoralis
Strongyloidiasis

- Exposure to contaminated faeces can result in transmission of this disease.

- The worm has an autoinfective cycle that allows infection to persist in the host indefinitely without the need for an external environment. Transformation of rhabditiform larvae into invasive filariform larvae in the gut of human host.
Strongyloidiasis

Increase number of larvae completing the autoinfectious cycle → large numbers of worms can enter the systemic circulation → hyperinfection syndrome.
Concept of hyperinfection and autoinfection
Hyper infection syndrome

Immunosuppression caused by:

- Iatrogenic: use of systemic corticosteroids
- Intercurrent illness ➔ HTLV-1/Human T cell Lymphotrophic Virus-1, organ transplantation

High risk of hyper infection syndrome in patients with strongyloidiasis
Impact of corticosteroid to parasite

- Corticosteroids (endogenous & exogenous) increase ecdysteroid like substances (naturally occurring non-hormonal anabolic effects) in the body mainly in the intestinal wall.

- Molting signals for eggs and rabditiform larvae

- Number of filariform larvae
Immunosuppression by Corticosteroid

Corticosteroids (endogenous & exogenous) affect the immunity by

• Increasing the apoptosis of Th2 cells
• Reducing the eosinophil count
• Inhibiting the mast cells response
Immunosuppression by Corticosteroid
<table>
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<tr>
<th>Type of immunity</th>
<th>Mediators</th>
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<tbody>
<tr>
<td>T cell mediated immunity</td>
<td>CD4+ T cells</td>
</tr>
<tr>
<td>Th2 cellular immunity</td>
<td>IL-4, IL-5</td>
</tr>
<tr>
<td>Humoral immunity</td>
<td>IgM, IgG, IgA, IgE</td>
</tr>
<tr>
<td>ADCC</td>
<td>IgM, IgG, Eosinophils, Neutrophils</td>
</tr>
<tr>
<td>Mucosal immunity</td>
<td>Mast cells, Goblet cells</td>
</tr>
</tbody>
</table>
Mucosal Immunity against Strongyloides sp

- Absence of CD4+ CD25+ T cells $\rightarrow$ Lack of cell activation in the mucosa $\rightarrow$ no change in jejunal morphology, different T cell subset numbers, mast cells, eosinophils and goblet cells, BUT a decrease of mature macrophages and dividing enterocytes in the crypts of intestinal walls $\rightarrow$ may preserve the architecture of mucosa and absence of immune mediated diarrhea.
Th2 role in strongyloidiasis

- IL-4: important regulator of IgE production & mast cell activation
- IL-5: innate immunity (induce eosinophil production, differentiation, maturation, survival) and adaptive immunity (IgM production by plasma cells)
- B cells: important role in subsequent challenge infections (increased parasite-speciespecific IgM)
- Specific IgE against filariform larvae: Protective role not clear, maybe useful for immunodiagnosis?
- ADCC (IgE activation of eosinophils & IgG activation of neutrophils) in strongyloidiasis: not effective against larvae?
In severe strongyloidiasis:

- Compared to asymptomatic or mildly symptomatic: lower levels of IgA, IgG, IgM.
- IgM specific for primary infective filariform larvae is not effective against autoinfective filariform larvae (have different surface antigens)
In severe strongyloidiasis:

• Eosinophils can cause destruction of helminth larvae esp. host-adopted filariform larvae, BUT not sufficient for complete protection

• Lower eosinophil counts in severe strongyloidiasis: suppression of eosinophils esp. in disseminated infections
Toxoplasma gondii

Toxoplasma gondii cyst in brain tissue

Toxoplasma gondii tachyzoites
Toxoplasmosis

• In people with AIDS, toxoplasmosis is most often due to reactivation of latent infection.

• 30% of HIV infected people with IgG positive develop toxoplasma encephalitis
Immune response

• The role of antibody and complement in the killing clearance of *T. Gondii* remain uncertain.

• Humoral response to *T. Gondii* includes the production of IgA, IgM, IgG, IgE.

• Cellular response appears significantly more important for the development of protective immunity.
Immune response

- The production of IL-12 precedes and initiates the synthesis of IFN-γ while the latter directly controls parasite growth and diminishes the contributions of Th-2.

- NK cells and CD8⁺ play a central role in the endogenous production of IFN-γ.
IFN-γ is an important mediator

• IFN-γ is a mediator inducing resistance of the host towards *T. Gondii*.

• There are two mechanism initiated by IFN-γ to inhibit the development of parasite:
  1. Nitric oxide (NO) production, Oxidative radicals
  2. Indoleamine 2,3 dioxygenase IDO production induces tryptophan degradation resulting in parasite stasis through lack of the essential amino-acid.
Cytokines involved in Toxoplasmic encephalitis

Animal model:
Th2 stimulate IL-4 & IL-10 production. IL-4 increase the number of cerebral cysts which leads to an increase in serum levels of IFN-γ, TNF-α, IL-6 and decrease TNF-α (due to IL-10).

The activation of macrophage induce IL-15 & IL-12 production: IL-12 induce a meningeal inflammation, IL-15 induce IFN-γ production by NK & T cell activation).

Low production of IL-7 in bone marrow & thymus induces cytotoxicity in NK cells while IL-7 leads to T-cell activation triggering the production of CD4-CD8.
Cytokines involved in Toxoplasmic encephalitis

Animal model:
Cerebral toxoplasmosis in HIV patients

- Decreasing or stopping of IFN-γ secretion in HIV-infected patients with lymphocytes CD4 <100/mm³ break the host-parasite balance

↓

- It can not control the disease (reactivation of the infection and development of encephalitis).
Two phenomena are responsible for the cerebral toxoplasmosis in HIV patients:

• A decrease of CD4 T cells will impact on the cellular response.

• An unbalance between Th1 and Th2 responses. The presence of IL-10 & IL-4 will decrease the production and activity of IFN-γ and the other protective Th1 cytokines.
Cerebral toxoplasmosis in HIV patients

• The cellular response reduce parasite’s multiplication.

• The humoral response is weakly protective against this intracellular parasite.