IMMUNITY TO PARASITIC AND FUNGAL INFECTIONS

• Chapter 20

Immunity to Malaria
• Immunity to sporozoites injected by mosquito
  – Mediated by antibody that prevents infection of liver cells

• Immunity to parasites in liver cells
  – Mediated by CD4+ and CD8+ T cells producing IFN-γ
  – Not lytic activity but IFN-γ prevents replication of parasite

• Immunity to parasites in red blood cells
  – Exponential growth stage and symptoms of disease
  – TH1 cells produce IL-2 and IFN-γ (proinflammatory cytokines)
    • Mφ activated and destroy infected RBCs
  – TH2 cells drive specific Ab production
    • blocks invasion of new RBCs
    • Destroys infected RBCs through complement activation
    • Enhances phagocytosis by Mφ through FcR

Topics Covered
• Overview of parasitic diseases
• Immune response to parasitic infections
• Immunity to malaria
• Immunity to schistosomiasis
• Immune effectors in parasitic infections
• How parasites evade the immune response
• General features of fungal pathogens
• Immunity to fungal infections

Immunity to Malaria
• Overproduction of TH1 cytokines
  – Important for parasite control
  – Produces life threatening complications of cerebral malaria, anemia, and other symptoms

• Sequestration of parasites in the brain leads to the production and release of proinflammatory cytokines
  – TH1 cytokines IFN-γ, IL-2, TNF, IL-1
  – Mediate the brain lesions and neurologic damage
  – NO produced by cerebral endothelium interferes with neurotransmission
**Dichotomy of protection and pathology associated with the TH1 response to Plasmodium**

- Malaria antigens
  - CD4+ T cell activation
  - TH1 cytokines (IL-2)
  - Parasite antigens
  - Low levels
    - Protection
  - High levels
    - Pathology
  - Inhibition of liver and blood-stage parasites
  - Demyelination
  - Erythrocytosis
  - Increased cytokine production
  - Macrophages
    - Inhibited
    - Expanded

**Immunity to Schistosomiasis**

- Correlative evidence:
  - High IL-4, IL-5, and IgE individuals remain unreinfected
  - High IFN-γ in individuals who were reinfected

- Disease is due to TH2-directed granulomatous response to worm egg antigens
  - B cells proliferate and produce IL-10
  - IL-10 stops costimulation of APCs
  - Downmodulates the size of the granuloma

**Immune Effectors in Parasitic Infections**

- Most important cytokine activated cell is the Mφ
  - In control and elimination of parasites

- Nitric Oxide (NO) main mechanism for Mφ killing of parasites
  - IFN-γ activates Mφ to generate NO
  - TNF-α also enhances NO production
  - TGF-β and IL-10 inhibit NO production

- Direct killing of schistosome larvae by IFN-γ activated Mφ

- ADCC killing of schistosome larvae by eosinophils and Ab IgE
  - Eosinophils use FcR to bind IgE coated larvae
  - Eosinophils degranulate and release ROI and other toxins that kill over 24 hours
Immune Effectors in Parasitic Infections: Schistosome larvae in vitro experiments

Immunity to liver stage of malaria
- Vaccination with irradiated sporozoites in the lab
  - Provides protection against reinfection
- Ab against sporozoites
- CMI to merozoites at liver stage
  - CTLs lyse infected liver cells
- TH1 cells produce IFN-γ
  - Inhibits growth of parasite inside the cell
  - Along with IL-6 (by liver cells), TNF, IL-1
- IL-6 and IFN-γ
  - induce production of NO by infected cells and liver Mφ (Kupffer cells)
  - Induce MHC class II on liver cells - killing by CD4+ cells also
- IL-6, IL-1, and TNF
  - induce liver cells to release C-reactive protein (CRP)
  - CRP binds to sporozoite and inhibits development to merozoite

Ab isotypes and parasitic infection
- Correlation between high IgE levels and disease symptoms in lymphatic filariasis (elephantiasis)
- Individual hosts with circulating microfilariae have high IgG4 and low levels of IgE
  - No disease symptoms
- Individual hosts that have cleared the microfilariae have high levels of IgE and low levels of IgG4
  - but exhibit elephantiasis
- Suggests IgE and not the parasite causes the lymphatic immunopathology
Cytokine and Ab profiles during lymphatic filariasis

![Diagram](image-url)


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**Immune evasion by parasites**

- Parasites have evolved many ways to evade host immune defenses
- Seclusion intracellularly
- Molecules that inhibit nonspecific host effector mechanisms
  - Complement
- Shield themselves with host derived molecules
- Antigenic variation of surface molecules
- Induce host cells to take on an immunosuppressive role

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**Immune evasion by parasites:**

**Seclusion intracellularly**

- Avoid antibody and complement by hiding inside cells
- Parasites use different independent strategies to avoid destruction within the cell
  - *Leishmania* activate complement and opsonization
    - Are taken up by macrophage, are enclosed in the phagolysosome
    - But produce antioxidant enzymes and inhibitors of lysosomal enzymes
  - *T. gondii* are taken up by phagocytes
    - Prevents phagosome from fusing with lysosome
  - *T. cruzi* (Chagas’ disease) not normal phagocytosis
    - Causes lysosomes to cluster and enter directly
  - *Trichinella spiralis* transform muscle cell to a specialized nurse cell
    - Only intracellular human helminth

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**Immune evasion by parasites:**

**Molecules that inhibit nonspecific host effector mechanisms**

- Activated immune cells
  - Produce hydrogen peroxide, superoxide ions, hydroxyl radicals that are toxic to pathogen
- Parasites produce antioxidant enzymes
  - Oxygen scavenging enzymes to protect themselves
  - Major enzymes are superoxide dismutase, catalase, and glutathione peroxidase
  - Superoxide dismutase is produced in extraordinary amounts by some parasites
- All protozoan and helminth parasites examined so far contain at least one of these antioxidant enzymes

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Immune evasion by parasites: Molecules that inhibit Complement

- Leishmania avoid membrane attack complex (MAC) by having extended surface proteins
  - that bind complement and induce phagocytosis of parasite
  - But do not allow MAC formation because they are too far away from the membrane surface
- T. cruzi express a molecule that prevents assembly of the complement cascade
  - No opsonization by complement and No MAC formation
- Shistosome larvae insert the host factor that normally blocks assembly of the complement cascade
  - No opsonization by complement and No MAC formation
- Taenia solium (pig tapeworm) produces paramyosin that blocks assembly of the complement cascade
  - No opsonization by complement and No MAC formation

Immune evasion by parasites: Antigenic variation of surface molecules

- Many examples by pathogens
  - the most dramatic is T. brucei (african sleeping sickness)
    - Entire surface is covered with a dense coating of a single protein called VSG (variant surface glycoprotein)
    - Waves of parasitemia correspond to a clonal population of parasites expressing a single VSG type
    - Antibodies are generated against this VSG and destroy the parasites
    - New clonal population arises with different VSG type and persist until a new antibody response is generated
    - Almost 1,000 genes encoding different variants of VSG
      - These genes are activated one at a time to effect antigenic variation
      - Gene switching occurs at a low spontaneous rate
      - At any given time, at least one parasite is likely expressing a different VSG than is targeted by antibody
        - can escape and cause another round of parasitemia

- Plasmodium falciparum (Malaria)
  - Antigenic variation of PfEMP1 expressed on surface of infected RBC
  - Lots of genes encode these proteins
    - 2-6% of the parasite genome
  - Variant switching occurs at a high rate
  - Emergence of new variants allows chronic infection
  - Explains why previously infected individuals can be reinfected
Immune evasion by parasites:
Antigenic variation of surface molecules

- T. cruzi, T gondii, and Leishmania induce expression of TGF-β
  - Downregulates both TH1 and TH2 responses
- T gondii, and Leishmania enter Mφ without inducing IL-12
  - No TH1 response
- Shistosome eggs induce IL-10
  - Diminishes IFN-γ mediated Mφ activation

Immunology of Fungal Infections

- Eukaryotic organisms that live on dead organic material
- Like bacteria, most are harmless
- Small number cause disease in humans
  - Called mycoses
- Common superficial infections to life threatening systemic diseases
  - Immunocompromised hosts
- Very difficult to treat
- Lack of effective safe anti-fungal drugs
- Amphoterin B is highly effective for systemic mycoses
  - Has serious side effects

Fungal Pathogens

- Different from “classical” parasites
- Do not depend on interaction with host for survival
- Only cause disease by accidentally infecting humans
- Fungi occur in 2 forms
  - Unicellular yeasts
  - Molds that grow in branching chains
    - Hyphae
- The most pathogenic fungal genera are
  - Aspergillus
    - Grow as molds
  - Cryptococcus, and Histoplasma
    - Grow as molds in nature and in vitro tissue culture plates
    - Grow as yeast-like budding cells in infected human tissue
Invasive pulmonary *Aspergillus* in a patient with Leukemia

*Aspergillus* on an agar culture plate

*Aspergillus* on an agar culture plate

*Cryptococcus neoformans* yeast cells in spinal fluid of AIDS patient with cryptococcus meningitis

*Cryptococcus neoformans* yeast cells in spinal fluid of AIDS patient with cryptococcus meningitis
Cryptococcus neoformans yeast cells in the liver of a patient with disseminated cryptococcus

Fungal Diseases

- Classified into 3 clinical groups
  1. Superficial mycoses
     - Most common infections
       - Skin, hair, and nails
       - Athlete’s foot and ringworm
     - Mucosal surfaces
       - *Candida albicans* normally present in mouth, vagina and intestinal tract
  2. Subcutaneous mycoses
     - Caused by puncture wounds
     - Localized abscesses
  3. Systemic mycoses
     - Histoplasmosis, cryptococcosis, and coccidioidomycosis
       - Begin as lung infections acquired by inhaling spores
       - Mild influenza-like symptoms
       - Fatal without treatment
         - At risk are immunosuppressed individuals
           - Chemotherapy, steroid therapy, AIDS patients

Innate immune responses to Fungi

- Physical barriers: skin and mucosa
- Chemical factors in serum and skin secretions
- Phagocytic and nonphagocytic cells
  - Neutrophils (PMNs) are most important phagocyte
- If these are insufficient
  - T cell mediated responses are required for effective control

Effector cells in fungal infections

- Phagocytic cells
- PMNs are most effective killers
- Drawn to site of fungal infection by chemotactic factors produced by fungus
- Or by fungal membrane activation of complement (not ab mediated)
- Fungi can stimulate IL-1 and TNF-α
  - Enhances infiltration of PMNs
- PMNS kill by
  - Oxygen dependent and independent mechanisms
**Effector cells in fungal infections**

- PMNS kill by Oxygen dependent
  - Generation of toxic chem via oxidative burst
  - Or release granules with enzymes that generate hypochlorous acid
- PMNS kill by Oxygen-independent mechanisms
  - Proteases
  - Defensins are antimicrobial peptides
- PMNs produce IL-12 and activate TH1 response
- NK cells directly by cytolysis granules and indirectly by activating Macrophages
- Alveolar Macrophages
  - Kill inhaled spores
  - Aspergillus are readily killed
  - Coccidioides and Histoplasma are resistant to Mφ killing
    - No phagosome/lysosome joining in Coccidioides
    - Histoplasma Grows within Mφ if they are not activated by specific immune response

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**ACQUIRED IMMUNITY TO FUNGAL INFECTIONS**

- TH cells and macrophages are important
- Probably little role for Ab
- TH1 response leads to disease resolution
  - IFN-γ and IL-12
- TH2 response leads to exacerbation of fungal infection
  - IL-4
- Show same responses in mice as Leishmania model

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**Dermatophyte immunity**

*Athlete’s foot, Ringworm*

- Infections that result in high inflammatory responses
  - are more likely to be cleared (TH1 response)
  - those that do not are more likely to be chronic (TH2 response)
- Dermatophyte antigens are important allergens?
  - If they elicit a TH2 response
  - Immediate type hypersensitivity
- Allergic bronchopulmonary aspergillosis
  - Have activated TH2 cells and asthma-like symptoms