Immunology to Fungal Infections

Introduction

- Various host defense mechanisms have evolved in humans to protect against fungal invasion
  - Innate
  - Adaptive responses
    - Antibody production (B cells/plasma cells)
    - T-cell mediated immunity (T cells)

- Outcome of host-fungus interaction is dependent upon the status of the host’s defenses

Introduction (cont.)

- Clinical manifestations of diseases depend upon:
  - Damage caused by the fungus
  - Damage caused by host inflammatory response
  - Damage caused by inflammation can be independent of invasion by the fungus

Innate Host Defenses

- Mechanical barriers
  - Skin
  - Mucous membranes
- Nutritional competition provided by bacteria
- Mucociliary clearance
- pH of body fluids
- Secretion of chemical antagonists
- Other mechanisms

Complement

- Composed of >30 serum proteins
- Augments (or “complements”) the antimicrobial activity of antibody
- Three major activities:
  - Defending against microbial infections
  - Bridging innate and adaptive immunity
  - Disposing of wastes
**Complement**
- Component of innate immune system
- Assists antibodies in clearing pathogens—"complement"
- Group of proteins which can be activated in cascade fashion to provide a humoral defense against microorganisms
- Considered a nonspecific defense, can be activated against specific microbes, that have been marked with antibodies
- Activated by antigen-antibody complexes, causes lysis
- Induces inflammation in order to initiate the healing process

**Neutrophils and Eosinophils**
- **Neutrophil**: the most abundant leukocyte (white blood cell) in the blood, helps to get rid of harmful microorganisms by engulfing them via phagocytosis
- **Eosinophil**: multifunctional leukocyte associated in the pathogenesis of asthma and immunity to certain organisms; also increase in number during allergic reactions
- Neutrophils help to get rid of fungal infections by engulfing and killing invasive fungal particles; after phagocytosis, they release neutrophil extracellular traps (NETs), which contain chromatin draped with antimicrobial proteins to trap and kill the fungal microbes
- Eosinophils increase in number when a fungal infection occurs in the body, to produce a defense against the microbes; they also release proinflammatory mediators, which allow the body to know there is a harmful infection occurring

**Dendritic Cells**
- Antigen (Ag) presenting cell
- Activate naïve T cell
- Follicular DC—maintain immune memory in tandem with B cells
- Maintain tolerance
- "In fungal infections DC cells have been shown to phagocytose in vitro and are important for protective immunity against the organism" (American Society for Microbiology)

**Macrophages**
- Macrophages are a type of white blood cells that ingests foreign material
- Macrophages are key players in the body’s first line of defense and their roles include:
  - Being phagocytes; their role is to engulf and digest cellular debris and pathogens (now commonly as phagocytosis)
  - The phagocytes use oxidative and non-oxidative mechanism that work synergistically to kill extracellular and internalized fungi

**Natural Killer Cells**
**Cytotoxic T-cells**
Function: Granzymes (proteins) form holes in target cell membrane forcing cell to perform apoptosis ultimately preventing fungal infection from spreading further.

**NK Cells**
- Component of innate immunity
- Kill infected cells by releasing granules of proteins
- Activated by cytokines and Fc receptors on surface

**Cytotoxic T-cells**
- Activated by 2 signal pathway during adaptive immune response
- Effector cells which mediate antibody dependent cell cytotoxicity and kill antibody coated target cells by binding with their receptors.
### CD4 and CD8 T Cells

- CD4 T cells: T cells that have the protein co-receptor CD4 on their surface; also called helper T (T\(H\)) cells.
- CD8 T cells: T cells that have the protein co-receptor CD8 on their surface; also called cytotoxic T (T\(C\)) cells.
- Function in defending against fungal infections:
  - CD4 T cells bind to MHC class II molecules on the surface of antigen-presenting cells, while CD8 T cells bind to MHC class I molecules on the surface of all nucleated cells.
  - Functional CD4 and CD8 cells are both required for effective elimination of fungal pathogens.
  - CD4 T cells make essential lymphokines that activate/recruit phagocytic cells to the sites of fungal infections.
  - CD8 T cells lyse infected cells and minimize tissue damage by reducing the inflammatory response.

### Antibody

- Part of specific host response
- Are glycoproteins generated by B cells
- Produced in response to fungal infections
  - inhibit adherence of fungi
  - reducing formation of biofilm
  - eliminates direct and indirect mechanisms
  - function as opsonins
  - promote fungal ingestions and killing by phagocytes
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