Foundations of Public Health
Immunology

Innate Immunity, Inflammation & Nutrition

Objectives
• Identify principles of innate immunity
• Identify receptors and responses of innate cells to microbes (alert system)
• Describe & identify examples of the 4 types of innate defensive barriers
• Identify the cardinal signs of inflammation
• Identify the differences between acute and chronic inflammation
• Identify components of inflammation & how they enhance immunity
• Understand role of nutrition in immune response & identify examples of nutrient deficiencies

Earliest Immune System
• Innate immunity refers to the basic resistance to disease that a species may possess
• Phylogenetically ancient defense
  • Invertebrates & vertebrates both have components of innate immunity (complement, receptors)
  • Only vertebrates contain adaptive responses

Principles of Innate Immunity
• Also known as Natural or Native immunity
• Provides general resistance to antigens
• Not specific for any given pathogen or antigen
  • Provides a rapid response to antigens
• No memory
  • Response does not improve with successive exposures to the same pathogen or antigen

Time is of the essence ...

The Battle Begins
• A microbe enters the body ...
• How does the innate system detect it?
• How does the innate system tell the rest of the body that there is a problem?
All About the Receptors: Recognition

- Innate response is not completely non-specific after all
- It recognizes PAMPs (Pathogen Associated Molecular Patterns)
- Toll-like receptors & Mannose receptors are part of our cellular membranes that recognize these PAMPs (e.g. LPS, mannose sugars on microbes)
- Receptors then send signals to the cell that a pathogen has entered & to turn up the immune response (alert – there is a problem!)

Bodily Harm Warning: Microbe Alert!

Innate Defenders: Overview

- Four types of defensive barriers:
  - Anatomic (skin, mucous membranes)
  - Physiologic (temperature, pH, oxygen, tension)
  - Phagocytic (macrophages, neutrophils ingest molecules)
  - Inflammatory (vasodilatation, capillary permeability)

Defensive Barriers: Anatomic

- Skin: major organ barrier (physical) against external organisms
  - Normal flora prevents colonization, constant sloughing of dead skin
  - Low pH and lysozyme are anti-microbial
- Mucous membranes: protects respiratory, genitourinary (GI), & urogenital tracts
  - Ciliated epithelial cells, mucous, tears, & saliva transport or kill microbes before they can colonize the body

Defensive Barriers: Physiologic

- Fever: pathogens grow at specific temps, and fever raises the body temperature above the preferred range
- pH: low pH in stomach, skin, vagina prevent infection
- Oxygen tension: skin wounds can lead to a decrease in localized tissue perfusion & hypoxia
  - Early innate immune system responds to hypoxia by activating nitric oxide synthase & inflammatory cytokines in wound
Defensive Barriers: Phagocytic

- Literal translation of phagocytosis is eating cell
- Specialized phagocytic cells
- Macrophages & Neutrophils
- Cell membrane folds in (endocytosis) & internalizes microbe to form a phagosome
- Fusion with lysosome + enzymes
- Intracellular killing with lysosomal enzymes, reactive oxygen intermediates (ROIs)

Innate + Adaptive

- Phagocytic cells are linked to adaptive responses
- Produce cytokines, costimulators that target T cells (enhanced antigen presentation)

Defensive Barriers: Inflammatory

- Macrophages release cytokines & ROIs that stimulate inflammation
- Neutrophils also stimulate macs & release ROIs to increase inflammation
- Inflammation enhances the immune response
  - Vasodilation & capillary permeability allow leukocyte migration to sites of tissue injury

Inflammation (-itis)

- The body’s reaction to invasion by an infectious agent, antigenic challenge or physical damage
- NONSPECIFIC response
- Major goal is to allow products of immune system into area of infection or damage

Inflammation

- Acute Inflammation
  - Temporary response to transient injury
  - May develop into chronic inflammation
  - Exudative response
- Chronic inflammation
  - Sustained reaction to persistent injurious stimulus
  - Proliferative response (involving cell-mediated immunity)
  - Granuloma formation may occur
Cardinal Signs of Acute Inflammation
1. Rubor: redness
2. Calor: heat
3. Dolor: pain
4. Tumor: swelling
5. Functio laesa: loss of function

Inflammatory Components
1. Blood supply changes
   - Increases to bring cells and large molecules to area
2. Capillary permeability changes
   - Increases to allow exudation of serum protein
3. Leukocyte migration
   - Increase into affected area across venules

Blood Supply Increase (1)

Capillary Permeability Changes (2)
**Leukocyte Migration (3)**

Cell Migration

- Leukocyte migration across endothelium depends upon:
  - Surface charge of the interacting cells (occurs where lowest)
  - Hemodynamic shear force in vascular bed (occurs where lowest)
  - Expression of adhesion molecules on leukocytes and endothelium
  - Pattern and purpose of migration depends on the cell type, state of differentiation and activation
  - Ensures the APCs, lymphocytes and antigen converge upon secondary lymphoid tissue, lymph nodes, or spleen to produce an immune response, or upon sites or inflammation

**Cells travel to infection site to destroy (4)**

Microbial Evasion Strategies

- Some bacteria have developed ways to defeat innate immunity
- Resist phagocytosis, ROIs to avoid death

<table>
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<th>Mechanism of immune evasion</th>
<th>Organism (example)</th>
<th>Mechanism</th>
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<tr>
<td>Resistance to phagocytosis</td>
<td>Pneumococcus</td>
<td>Capsular polysaccharide (EPS) phagocytosis inhibition</td>
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<td>Resistance to reactive oxygen intermediates in phagocytes</td>
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<td>Production of catalase, which inactivates reactive oxygen species</td>
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<td>Resistance to complement activation (alternative pathway)</td>
<td>Neisseria meningitides</td>
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<td>Resistance to antimicrobial peptide antibiotics</td>
<td>Pseudomonas</td>
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**Role of Nutrition in Immunity**

- Nutrition is a key element to a healthy immune system
- Vitamin deficiencies have been shown to decrease immune function
- And, lead to increased infections

**Extremely Brief Review of HUMAN NUTRITION**

- FOOD is a mixture of chemicals
- NUTRIENTS are the essential chemicals in foods
- 6 classes of nutrients found in food:
  - Carbohydrates
    1) Lipids
    2) Proteins
    3) Vitamins
    4) Minerals
    5) Water
Macronutrients vs. Micronutrients

**Macro**
- Nutrients such as carbohydrates, fat, or proteins, that are needed in relatively large amounts in the diets
- Enables body to produce enzymes, hormones & other substances essential for proper growth and development
- Vitamins A, C, D important to properly functioning immune system
- Zinc & iron

**Micro**
- Nutrients such as a vitamin or mineral that is needed in relatively small amounts in the diet
- Fruits and Veggies are important sources of nutrients, especially micronutrients. Photo by Peggy Greb, USDA Image Number K8666-1

Malnutrition: The Silent Crisis

**Definition:** Failure to achieve nutrient requirements which can impair physical and/or mental health

- May result from consuming too little food or a shortage/imbalance of key nutrients
- Several types:
  - Protein-energy malnutrition (PEM)
  - Kwashiorkor
  - Marasmus
  - Micronutrient deficiencies (Vitamins A, C, D)
  - Mineral deficiencies (Zinc, Iron)

Protein-Energy Malnutrition (PEM)

- Most widespread form of malnutrition
- Prevalent in Africa, Central & South America, East
- Condition of infants and children
- Develops after children are weaned from the breast
- Micronutrient deficiencies linked to development of PEM
- Widespread atrophy of lymphoid tissues & 50% reduction in circulating CD4+ T cells

Marasmus

- A type of malnutrition resulting from chronic protein-energy under nutrition characterized by wasting of muscle and other body tissue
- Physical term for starvation
- Often occurs after child weaned from breast milk

Kwashiorkor

- Type of malnutrition that occurs primarily in young children who have an infectious disease
- Diets supply marginal amounts of energy and very little protein (carbs ↑)
- Common symptoms include poor growth, edema, apathy, weakness, & susceptibility to infections
- Diarrhea & anemia compound problem

Vitamin A

- Vitamin A need for
- Vision (night, day, color)
- Epithelial cell integrity (against infections) in skin, mucous membranes
- Immune response
- Haemopoiesis
- Skeletal growth
- Fertility (male and female)
- Embryogenesis
### Vitamin A Deficiency

- More than one million children a year die as a consequence of a number of diseases precipitated by VAD.
- All developing countries affected by multiple micronutrient deficiencies, but vitamin A highly impacts Africa and SE Asia.

### Vitamin A Deficiency

- VAD prevalent among poor who depend mainly on rice as daily energy source (400 million).
- Rice does not contain β-carotene (provitamin A).
- Most severely affects children and pregnant women.
- Compromises immune systems of ~40% of children <5.
- Predisposes infants and children to diarrheal disease.
- Usually co-existing with PEM.
- 250,000 to 500,000 children go blind every year.
- More than half also die with a year.

### Vitamin C

- Vitamin C helps maintain the redox integrity of cells.
  - Protects against reactive oxygen species generated during respiratory burst and in the inflammatory response.
  - Shown to reduce the duration and severity of colds (Mom is right – drink your Orange Juice!)
- Vitamin C supplementation improves immune function:
  - Antimicrobial and natural killer cell activities.
  - Lymphocyte proliferation.
  - Chemotaxis.
  - Delayed-type hypersensitivity.
- Vitamin C modulates host resistance to infectious agents, by reducing risk, severity and duration of infectious diseases.

### Vitamin D

- Humans make Vitamin D in skin – need sunlight.
- Also produced by activated macrophages.
- Vitamin D is an important immune regulator.
- Deficiency results in overactive response & has been linked to some autoimmune diseases.

### Zinc & Iron

- Zinc important to biological activity of thymus hormones.
  - Deficiency results in decreased cell-mediated immunity.
  - Impairs phagocytosis, NK cell activity, and generation of oxidative burst.
- Iron extremely important to cellular functions & oxygen transport.
  - Deficiency impairs oxidative burst in neutrophils.

### Malnutrition and Infection

- Two causal pathways:
  1. Infection leads to malnutrition.
  2. Malnutrition increases susceptibility to infections.
- Difficult to resolve, pathways may occur concurrently.
- Nutrition improves immunity – eat a balanced diet!
Summary of Innate Immunity

- Understand principles of innate immunity
- Innate receptors & signaling networks
- Four innate defensive barriers
- 4 stages of inflammation after tissue damage
- Role of nutrition in immune response
- Specific examples of vitamin deficiencies & immune function

Self-Test Questions

- Name 2 characteristics of innate immunity (principles).
- How does the innate immune response recognize pathogens?
- What are the 4 types of defensive barriers? Give an example of each type.
- What is the difference between acute & chronic inflammation?
- What are the 5 cardinal signs of inflammation?
- What are the 3 major components of the inflammatory response?
- How does nutrition influence the immune response? Give 2 examples of the impact of vitamin deficiencies on immunity.