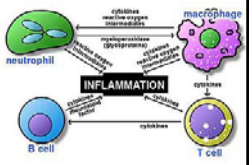
Foundations of Public Health Immunology

Innate Immunity, Inflammation & Nutrition



1

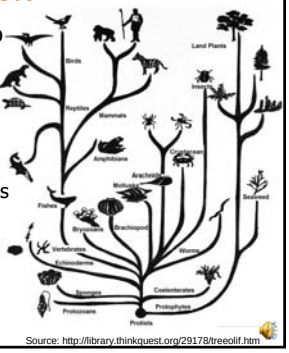
Objectives

- 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

2

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



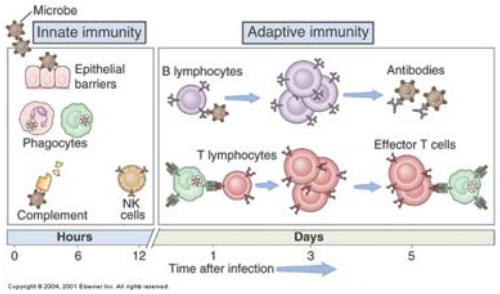
Source: http://library.thinkquest.org/29178/treeolif.htm

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

4

Time is of the essence…



The Battle Begins

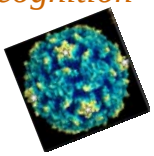
- A microbe enters the body…
- How does the innate system **detect** it?
- How does the innate system tell the rest of the body that there is a problem?

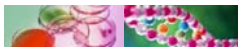
6

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!)

Watch this animation that shows how TLRs recognize a virus to protect the body.



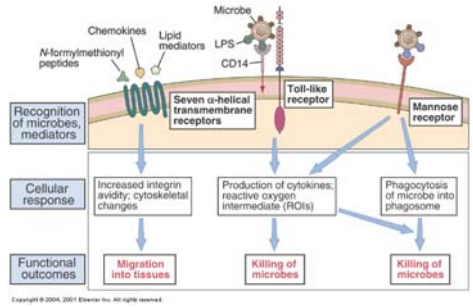


Read this brief NY Times article on the therapeutic history of Toll-like receptors and how drug companies are now using Toll-like receptors as designer drugs.

7

Bodily Harm Warning: Microbe Alert!

Watch this short flash animation that shows the activation of the immune cell as it responds to LPS binding to a Toll-like receptor.



8

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)

Watch a quick flash animation of how innate immunity defends against microbes @ Innate Immune System

9

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

10

Defensive Barriers: Anatomic

- Mucous membranes:
  - Chemical: mucous traps or prevents microbial attachment to cells
  - Enzymes: lysozyme degrades G+ cell wall and is present in tears & saliva; proteases destroy cell membrane of G- bacteria & viral envelope coats

11

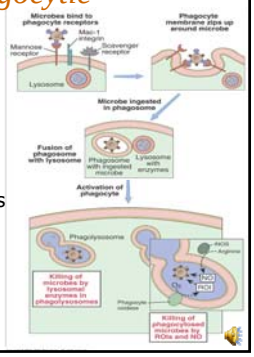
Defensive Barriers: Physiologic

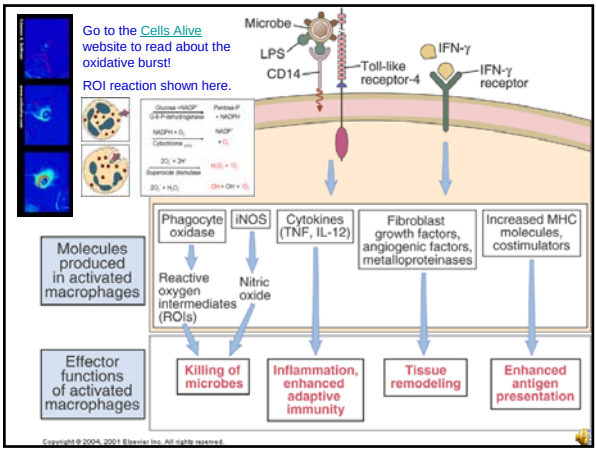
- Fever: pathogens grow at specific temps, and fever raises the body temperature above the preferred range
- pH: low pH in stomach, skin, vagina prevent infection
- Oxygen tension: skin wounds can lead to a decrease in localized tissue perfusion & hypoxia
  - Early innate immune system responds to hypoxia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

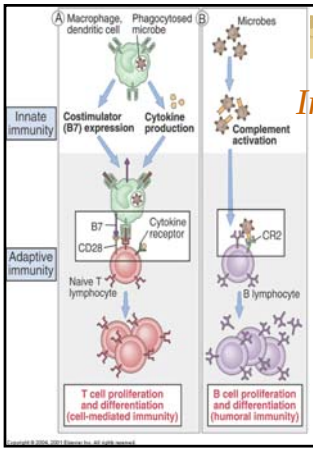
12

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)**







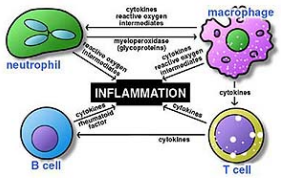
Innate + Adaptive

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

15

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



Source: http://www.glycoscience.com/glycoscience/start_frames.wm?FILENAME=G004&MAIN=glyconutritionals&SUB=disease

16

Inflammation (-itis)

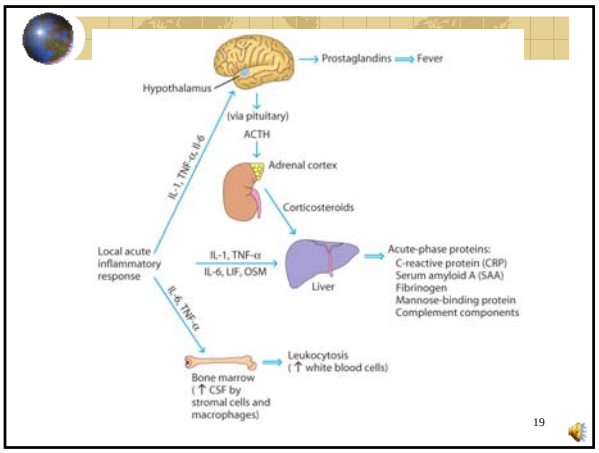
- The body's reaction to invasion by an infectious agent, antigenic challenge or physical damage
- **NONSPECIFIC** response
- Major goal is to **allow products of immune system into area of infection or damage**

Watch this brief intro video to inflammation: Is it a good thing or a bad thing? Beware: swollen feet!

17

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

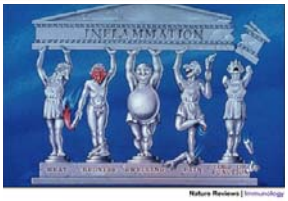


Image Source: Nature Reviews Immunology 2, 787-795 (2002); doi:10.1038/nri915 ANTI-INFLAMMATORY LIPID MEDIATORS AND INSIGHTS INTO THE RESOLUTION OF INFLAMMATION

- 1. Rubor: redness
- 2. Calor: heat
- 3. Dolor: pain
- 4. Tumor: swelling
- 5. Functio laesa: loss of function

Click through these slide shows on Acute Inflammation & Cardinal Signs to see images of the cardinal signs of inflammation.

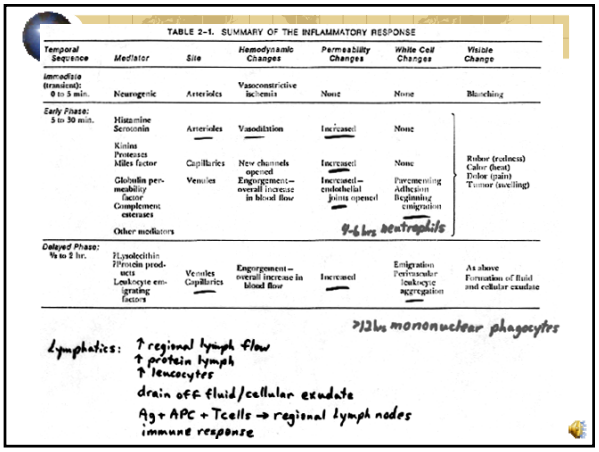


TABLE 2-1. SUMMARY OF THE INFLAMMATORY RESPONSE

Temporal Sequence	Mediator	Site	Hemodynamic Changes	Permeability Changes	White Cell Changes	Visible Change
Immediate (transient): 0 to 5 min.	Neurogenic	Arterioles	Vasoconstrictive ischemia	None	None	Blanching
Early Phase: 5 to 30 min.	Histamine Serotonin	Arterioles	Vasodilation	Increased	None	Rubor (redness) Calor (heat) Dolor (pain) Tumor (swelling)
	Kinins Proteases Miles factor	Capillaries	New channels opened	Increased	None	
	Globulin permeability factor Complement enzymes	Venules	Engorgement—overall increase in blood flow	Increased—endothelial joints opened	Parenchymal Adhesion Beginning emigration	
	Other mediators			4-6 hrs neutrophils		
Delayed Phase: ½ to 2 hr.	Hydrolecithin Protein products Leukocyte emigrating factors	Venules Capillaries	Engorgement—overall increase in blood flow	Increased	Emigration Perivascular leukocyte aggregation	As above Formation of fluid and cellular exudate

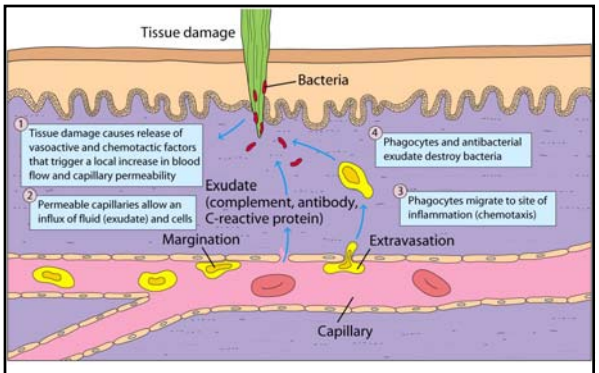
>12hr mononuclear phagocytes

Lymphatics: ↑ regional lymph flow
↑ protein lymph
↑ leucocytes
drain off fluid/cellular exudate
Ag + APC + Tcells → regional lymph nodes
immune response

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

22



Blood Supply Increase (1)

23

Capillary Permeability Changes (2)

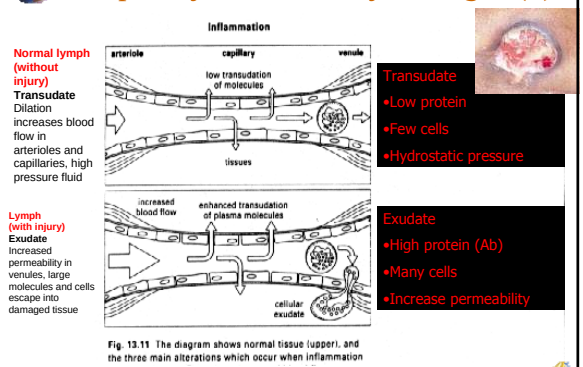


Fig. 13.11 The diagram shows normal tissue (upper), and the three main alterations which occur when inflammation

Normal lymph (without injury)
Transudate
Dilation increases blood flow in arterioles and capillaries, high pressure fluid

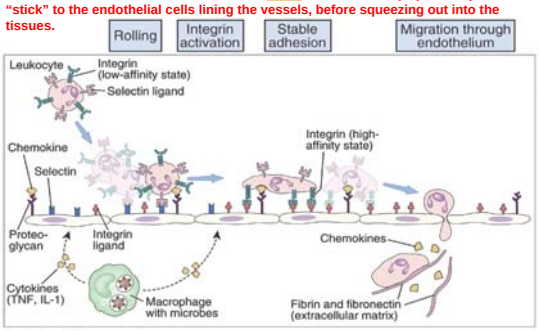
Lymph (with injury)
Exudate
Increased permeability in venules, large molecules and cells escape into damaged tissue

Transudate
- Low protein
- Few cells
- Hydrostatic pressure

Exudate
- High protein (Ab)
- Many cells
- Increase permeability

Leukocyte Migration (3)

Watch an animation of how immune cells move to the site of injury, as they roll & "stick" to the endothelial cells lining the vessels, before squeezing out into the tissues.

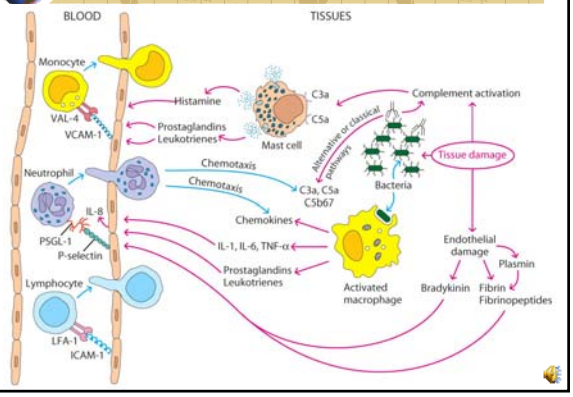


Cell Migration

- 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 upon the cell type, state of differentiation and activation
- Ensures that APCs, lymphocytes and antigen converge upon secondary lymphoid tissue, lymph nodes, or spleen to produce an immune response, or upon sites of inflammation

26

Cells travel to infxn site to destroy (4)



Microbial Evasion Strategies

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

Mechanism of immune evasion	Organism (example)	Mechanism
Resistance to phagocytosis	*Pneumococcus*	Capsular polysaccharide inhibits phagocytosis
Resistance to reactive oxygen intermediates in phagocytes	Staphylococci	Production of catalase, which breaks down reactive oxygen intermediates
Resistance to complement activation (alternative pathway)	*Neisseria meningitides*	Sialic acid expression inhibits C3 and C5 convertases
	Streptococcus	M protein blocks C3 binding to organism and C3b binding to complement receptors
Resistance to antimicrobial peptide antibiotics	*Pseudomonas*	Synthesis of modified LPS that resists action of peptide antibiotics

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

29

Extremely Brief Review of HUMAN NUTRITION

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

30

Macronutrients vs. Micronutrients

Macro

- Nutrients such as **carbohydrates, fat, or proteins**, that are needed in relatively large amounts in the diets

Micro

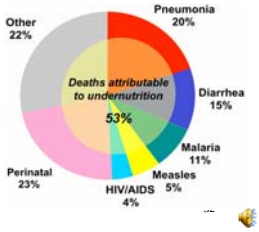
- Nutrients such as a **vitamin or mineral** that is needed in relatively small amounts in the diet
- Enables body to produce enzymes, hormones & other substances essential for proper growth and development
- Vitamins A, C, D important to properly functioning immune system
- Zinc & iron

Fruits & Veggies are important sources of nutrients, especially micronutrients. Photo by Peggy Greb, USDA Image Number K8666-1.

31

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

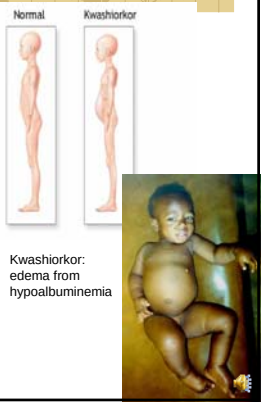
33

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

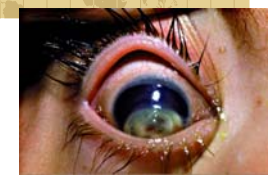
- Type of malnutrition that occurs primarily in **young children who have an infectious disease**
- Diets supply marginal amounts of energy and very little protein (carbs ↑)
- Common symptoms include poor growth, edema, apathy, weakness, & **susceptibility to infections**
- Diarrhea & anemia compound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



Kwashiorkor: edema from hypoalbuminemia

Vitamin A

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



Keratomalacia, damage shows a softened hyperkeratotic epithelium and may thus become secondarily infected.

36

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**

37

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 to go blind every year
  - More than half also die within a year

38

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

39

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

40

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

41

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!

42

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

43

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.

44