

**Innate Immune Response****Lecture Outline****2/14/01**

No memory. The innate immune response is very important for activating the adaptive immune system. Innate immune responses can activate inflammation as a danger signal that something has damaged host tissue.

**I. Components of the innate immune system**A. Physical and chemical barriers

B. Complement (C') is a group of serum proteins that participate in an enzymatic cascade ultimately generating the cytolytic membrane-attack complex.

C. CytokinesChemokines and Interferons ( $\alpha/\beta$  IFNs).D. Phagocytic cells

Neutrophils and Macrophages

Neutrophils have a short lifetime and are the predominant phagocytic cell in acute infections. Macrophages are larger than neutrophils, have a longer lifetime, and predominate in chronic infections.

E. Natural killer (NK) cells.

1. Kill virally infected cells and tumor cells.
2. Increased activity in response to IFN- $\alpha$  and  $\beta$ , TNF- $\alpha$ , IL-12.
3. Produce IFN- $\gamma$  when activated.
4. NK cells are lymphocytes, but do not have antigen-specific receptors.

**II. Innate immune response varies with pathogen**Portal of entry.Location for replication/infection.Size and complexity of pathogen.

Protection against extracellular pathogens includes; barriers, phagocytic cells, complement, and antibody. Protection against intracellular pathogens includes; barriers, interferons, NK cells, cytotoxic T cells, and antibody for extracellular phases of viral life cycle only.

**III. Inflammation****A. Mechanism of Acute Inflammatory Response**

3 Steps to initiate inflammatory process.

1. Vasodilation which is an increase in the diameter of blood vessels.
2. Increased capillary permeability which allows for the influx of fluid from capillaries into tissue.
3. Extravasation of cells. Immune cells exiting bloodstream into tissues of as a result of the activated endothelium and increased capillary permeability.

**Neutrophil extravasation.**

Vascular addressins are CAMs expressed on endothelium that indicate a site of inflammation and control Neutrophil movement into tissues from bloodstream. .

Chemoattractants : (such as the chemokine IL-8, and Complement product C3a) act on Neutrophils attracting them to site of inflammation.

**Central Role for Neutrophils in activating acute inflammation.**  $10^{11}$  in body.

Short lived cells which can increase in numbers during acute inflammation.

## 1. Mediators released from granules.

- a) Reactive oxygen intermediates (ROIs). ( $O_2^-$ ,  $H_2O_2$ ), reactive nitrogen (NO), and hydroxyl free radical (OH).
- b) Enzymes proteases, phospholipases, collagenases which kill pathogens and lyse cells.

Lysozyme which splits the proteoglycan cell wall of bacteria.

These anti-microbial enzymes and reactive molecules are produced and used inside the cells especially in lysosomes. But they can be released from granules to kill extracellular microorganisms and cause tissue damage. The dead neutrophils along with dead epithelial cells and dead microorganisms form pus.

2. Phagocytosis and enhanced phagocytosis through opsonization..
3. Release cytokines/chemokines that activate innate and adaptive immunity.

### **Role of Macrophages in Acute Inflammation**

Monocytes in circulation mature into resident tissue macrophages. In the absence of inflammation macrophages are concentrated in connective tissue, GI tract, lung, liver, spleen.

Macrophages become activated by phagocytosis of particulate antigen. Macrophages have many receptors to bind bacterial cell wall components such as LPS, hemagglutinin which trigger phagocytosis. In addition they can take up antigen through opsonization (binding through CRs and FcRs).

### **B. Mediators of inflammation**

1. Cytokines. Pro-inflammatory cytokines: IL-1, TNF- $\alpha$ , IL-6.  
Chemokines.
2. Plasma enzyme activators. Kinins. Bradykinin is a vasoactive peptide.
3. Complement. C3a, C4a, C5a are byproducts of complement that activate inflammatory response.
4. Lipid inflammatory mediators. (Arachidonic acid metabolites).

### **IV. Chronic Inflammation**

Chronic inflammation is characterized by the presence of macrophages and is maintained by T cell immune responses to antigens.

1. Infectious agent persisting
2. Autoimmunity
3. Delayed type hypersensitivity (DTH)
4. Cancer--tissue damage--leads to chronic inflammation.

### **V. Acute Phase Response and Systemic Inflammation**

The acute phase response (APR) is regulated by the central nervous system (CNS) and activated by acute phase proteins produced in liver. If localized inflammatory responses do not contain the injury, infection, or irritation ("stress") the APR is an emergency reaction that represents a switch of the immune system from the specific reactivity of T cells to less specific systemic activation of innate (non-specific) immune responses including fever.