

## Chapter 15 Non Specific Defense of the Host

### I. Host Defense Mechanisms

#### A. Resistance

1. The ability to ward off disease. It is the result of genetically predetermined (innate) resistance and other factors such as the individual's age, sex, and nutritional status.
2. **Constitutive Defenses:** Defenses common to all healthy animals. These defenses provide general protection against invasion by normal flora, or colonization, infection, and infectious disease caused by pathogens. The constitutive defenses have also been referred to as "natural" or "innate" resistance, since they are inherent to a specific host, but these terms are better reserved for certain types of constitutive defenses.

#### **Absence of specific tissue or cellular receptors for attachment (colonization) by the pathogen.**

For example, different strains of enterotoxigenic (Shiga toxin) *E. coli*, defined by different fimbrial antigens, colonize human infants, calves and piglets, by recognizing species-specific carbohydrate receptors on enterocytes in the gastrointestinal tract.

#### **Temperature of the host and ability of pathogen to grow.**

For example, birds do not normally become infected with mammalian strains of *Mycobacterium tuberculosis* because these strains cannot grow at the high body temperature of birds. The anthrax bacillus (*Bacillus anthracis*) will not grow in the cold-blooded frog (unless the frog is maintained at 37°C).

#### **Lack of the exact nutritional requirements to support the growth of the pathogen.**

Naturally-requiring purine-dependent strains of *Salmonella typhi* grow only in hosts supplying purines. Mice and rats lack this growth factor and pure strains are avirulent. By injecting purines into these animals, such that the growth factor requirement for the bacterium is satisfied, the organisms prove virulent.

#### **Lack of a target site for a microbial toxin.**

Most toxins produced by microbial cells exert their toxic activity only after binding to susceptible cells or tissues in an animal. Certain animals may lack an appropriate target cell or specific type of cell receptor for the toxin to bind to, and may therefore be non-susceptible to the activity of the toxin. For example, injection of diphtheria toxin fails to kill the rat. The unchanged toxin is excreted in the urine. Inject a sample of the urine (or pure diphtheria toxin) into the guinea pig, and it dies of typical lesions caused by diphtheria toxin.

3. Susceptibility is lack of resistance.

## B. Predisposing factors

1. Age, fatigue, stress, and poor nutrition, all of these factors can make a host more susceptible to infection and disease.

These factors include:

- a. Natural host resistance: skunk are more susceptible to rabies than opossum.
- b. Age, stress and diet: the very young and old, alike, have weaker immune systems.
- c. Anatomical defenses: Skin is a great barrier to microbes. Other aspects of skin include skin pH from oxidizing oil, lysozymes of perspiration and tears from the eye,

## C. Nonspecific defenses:

1. (e.g., fever, inflammation) are used to protect the body from all kinds of pathogenic organisms. They generally serve as a first line of defense.
2. Nonspecific defenses include mechanical barriers such as skin, saliva, the lacrimal apparatus, and mucous membranes, as well as the outward flow of urine, vaginal secretions, and blood (from wounds). Phagocytosis, fever, inflammation, and molecular strategies.

## D. Specific defenses include:

1. Specific defenses refer to immunity or the characteristic response of the host to a foreign invader or antigen. This response is called the immune response

## II. Mechanical Factors

### A. Skin

1. Two distinct portions to skin: dermis and epidermis
  - a. Epidermis is usually dry and by periodic shedding of epidermis skin cell microbes can become established.
    - 1) Except for hot humid climates where fungal infection can be established
  - b. Staphylococci normally inhabit the epidermis, hair follicles, and sweat and oil glands of the skin

### B. Mucous membranes

1. Line the gastrointestinal, respiratory and genitourinary tracts of the body
  - a. mucous prevents the tracts from drying out
    1. Washes microbes from surface prior to establishment
  - b. Stomach is very acidic killing most microbes: Small intestine is alkaline discouraging microbe establishment - bile salts and lysozyme will kill or inhibit many type of bacteria
  - c. Some pathogens live in mucous environment: *Treponema pallidum*

### C. Lacrimal apparatus

1. Eye protection
  - a. a group of structures that manufactures and drains away tears.
  - b. Tears wash away microbes keeping the eye healthy
- c. Large amounts of lysozyme and phospholipase produced to protect eye.
  - 1) These agents breakdown the cell wall of bacteria and destabilize bacterial membranes.

### D. Saliva

1. Dilutes and washes away bacterial from teeth

### E. Cilia of the lungs

1. Ciliary escalator: move mucus from lung to upper throat at about 1 - 3 cm/hr.
2. Coughing and sneezing also eliminate bacteria.

### F. Urine

1. Cleansing of urethra tract by urine flow

### H. Vaginal secretions.

1. Moves microorganisms out of the female body.
2. Vaginal epithelium of female body maintains a high population of *Lactobacillus acidophilus* - acid producer.

## III. Chemical Factors.

Chemical factors when combined with mechanical factors (skin barrier) play an important role

### A. Sebum

1. Oils produced by the glands of the skin
2. Forms protective layer over the skin's surface
  - a. Component of Sebum is fatty acid
  - b. When fatty acids break down they lower skin pH to a range between 3 to 5.

### B. Perspiration

- 1.a. Sweat glands not only maintain temperature but aid in elimination of certain wastes and flush microorganisms
2. Perspiration also contains Lysozyme
  - a. Lysozyme break down cell walls of gram positive, and to a lesser extent, gram negative bacteria
  - b. peptidoglycan bonds broken

### C. Low pH (5.5 and lower) of sweat and gastric secretions

- 1) prevents growth of bacteria.

D. Defensins (low molecular weight proteins)

- 1) found in the lung and gastrointestinal tract have antimicrobial activity.

E. Surfactants in the lung

- 1) act as opsonins (substances that promote phagocytosis of particles by phagocytic cells).

F. Lactoferrin and transferrin

- 1) Binds iron
  - a. an essential nutrient for bacteria, these proteins limit bacterial growth

#### IV. Normal Microbiota and Nonspecific Resistance

A. Competition with non-indigenous species for colonization sites.

B. Specific antagonism against non-indigenous species.

- a. normal flora bacteria produce bacteriocins which kill or inhibit closely - related species of bacteria

- 1) *E. coli* in the large intestine which produces bacteriocins that inhibit the growth of *Salmonella* and *Shigella*

C. Nonspecific antagonism against non-indigenous species

1. normal flora produce a variety of metabolites and end products that inhibit other microorganism.

- a. In the vagina alters pH to prevent overpopulation by *Candida albican*, a pathogenic yeast that causes vaginitis.

2. Commensalism

- a. One organism uses the body of a larger organism as its physical environment and may make use of the body to obtain nutrients.

- b. Opportunistic pathogens

1. Opportunists are considered to be of low virulence

- a) They are commonly members of the normal flora
- b) Normally microbes are harmless, but may cause disease if their environmental conditions change:
- c) They produce infection only when introduced into a normally sterile body site, when populations of flora are upset, or in immuno-compromised hosts

2. Opportunism increases with increasingly latent infection rates
  - a) Opportunistic microbes include *E. Coli*, *Straphylococcus aureus*, *S. Epidrmidis*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, and oral streptococci.

## V. Phagocytosis

A. There are three categories of white blood cells (**leukocytes**):

1. the granulocyte (neutrophils, basophils, eosinophils), which predominate early in infection
2. the monocytes, which predominate late in infection
3. and the lymphocytes.

### B. White Blood Cells

Neutrophils	60-70%
Basophils	0.5-1%
Eosinophils	2-4%
Monocytes	3-8%
Lymphocytes	20-25%

Percentage of each type of white cell in a sample of 100 white blood cells

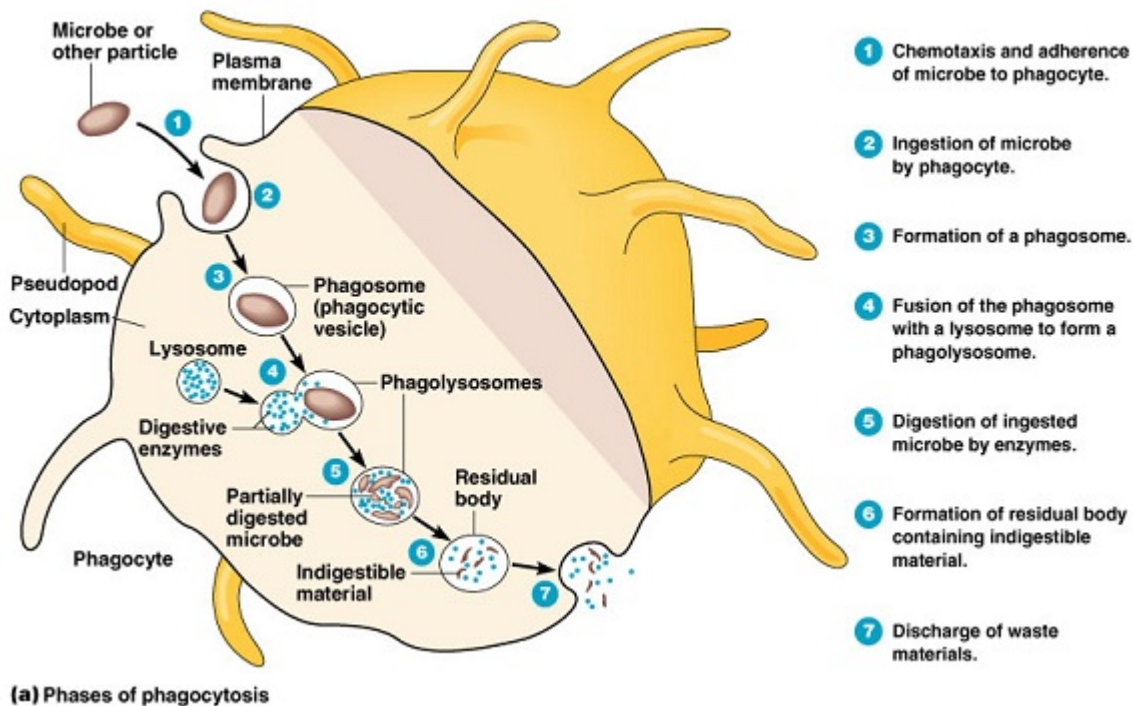
1. Neutrophils: Phagocytic
2. Basophils: Produce histamine (not much is known)
3. Eosinophils: Toxic to parasites some phagocytosis
4. Monocytes: Phagocytic as mature macrophages
5. Fixed macrophages*
6. Wandering macrophages roam tissues (dendritic cells)
7. Lymphocytes: Involved in specific immunity

5.* Fixed Macrophages	
Name of cell	Location
Dust cells/Alveolar macrophages	pulmonary alveolus of lungs
Histiocytes	connective tissue
Kupffer cells	liver
Microglia	neural tissue
Epithelioid cells	granulomas
Osteoclasts	bone
Sinusoidal lining cells	spleen
Mesangial cells	kidney

### C. Mechanism of Action

Phagocytosis is the cellular ingestion of a foreign substance (including microorganisms). Certain types of white blood cells (including neutrophils and monocytes in the blood, and fixed and wandering macrophages) are phagocytes

Phagocytes locate microorganisms through **chemotaxis**. They then adhere to the microbial cells, a process that is sometimes facilitated by **opsonization**, wherein the microbial cell is coated with plasma proteins. Pseudopods then encircle and engulf the microbe. The phagocytized microbe, enclosed in a vacuole called a phagosome, is usually killed by lysosomal enzymes and oxidizing agents (such as superoxide radical, hydrogen peroxide, singlet oxygen and hydroxyl radicals).



### C. Stages of Phagocytosis

1. Chemotaxis of phagocyte to microbes
2. Adherence of microbe by macrophage
3. Ingestion of microbes by phagocytes
4. Killing of microbes by enzymes and chemical agents
5. Elimination

#### D. Evasion of Phagocytosis

##### 1. M protein and capsules

- a. *Streptococcus pyogenes* M protein inhibits phagocytes adherence to their surface
- b. *Streptococcus pneumoniae* and *Haemophilus influenzae* type b use capsules to evade phagocytosis

##### 2. Other microbes can be ingested but not killed

- a. Staphylococcus produces leukocidins that may kill the phagocytes
- b. Streptolysin produced by streptococci has a similar mechanism of action

##### 3. Pathogens secrete membranes

- a. American trypanosomiasis and *Listeria monocytogenes* produce membrane attack complexes that lyse phagolysosome membranes and release the microbes into cytoplasm of the phagocyte

##### 4. Survive inside phagocyte

- Coxiella burnetti* requires low pH of phagolysosome

#### E. Initiation of Phagocytosis

1. Fc receptors Bacteria with IgG antibody on their surface have the Fc region exposed and this part of the Ig molecule can bind to the receptor on phagocytes. Binding to the Fc receptor requires prior interaction of the antibody with an antigen. Binding of IgG-coated bacteria to Fc receptors results in enhanced phagocytosis and activation of the metabolic activity of phagocytes (respiratory burst).
2. Complement receptors Phagocytic cells have a receptor for the 3rd component of complement, C3b. Binding of C3b-coated bacteria to this receptor also results in enhanced phagocytosis and stimulation of the respiratory burst.
3. Scavenger receptors Scavenger receptors bind a wide variety of polyanions on bacterial surfaces resulting in phagocytosis of bacteria.
4. Toll-like receptors of phagocytic cells have a variety of Toll-like receptors (Pattern Recognition receptors or PRRs) which recognize broad molecular patterns called PAMPs (pathogen associated molecular patterns) on infectious agents. Binding of infectious agents via toll-like receptors results in phagocytosis and the release of inflammatory cytokines (IL-1, TNF-alpha and IL-6) by the phagocytes

#### IV. Inflammation

##### A. Description

1. Inflammation is a response to cell damage. Initiation of inflammation is caused by the release of histamine, kinins, and prostaglandins.

B. Four signs and symptoms:

Redness, heat, swelling, pain, and sometimes loss of function are characteristic of inflammation.

C. Acute vs. chronic inflammation

1. If inflammatory cause is removed in short time, the inflammatory response may be intense (acute inflammation)
2. Longer lasting less intense (overall more destructive) is referred to as a chronic inflammation

D. Mechanism of action

1. Redness
2. Pain
  - a. caused by nerve damage, irritation by toxins or the pressure of edema
3. Heat
4. Acute-phase proteins activated (complement, cytokine, kinins)
5. Vasodilation (histamine, kinins, prostaglandins, leukotrienes)
  - a. localized collection of pus (a mixture of dead cells and body fluids)
  - b. Tissue injury also stimulates blood clotting, which may help to prevent dissemination of the infection.
6. Margination and emigration or migration (Diapedesis) of WBCs
  - a. Neutrophils and monocytes stick to the inner surface of endothelium of blood vessels.
  - b. This process is called margination
  - c. Emigration: Phagocytes squeeze between the endothelial blood vessel to reach the damaged area to destroy invading microorganisms by phagocytosis.
  - d. Task accomplished by chemotaxis
7. Tissue repair
  - a. Final stage is tissue repair
    - 1) dead cells removed and or replaced.
    - 2) harmful substances removed or neutralized at the site of injury.



## VI. Fever

Inflammation is a local response of the body to injury.

A systemic response to inflammation is Fever

A. Fever is abnormally high body temperature produced in response to infection. It serves to augment the immune system, inhibit microbial growth, increase the rate of chemical reactions, raise the temperature above the organism's optimum growth temperature, and decrease patient activity. Fever is considered a defense mechanism.

1. Gram (-) endotoxin cause phagocytes to release interleukin 1 (IL-1)
  2. Interleukin-1 (IL-1) signals hypothalamus of brain to release prostaglandin resetting the hypothalamic thermostat raising the body temperature from 37°C to 39°C
    - a. Alpha tumor necrosis factor produced by macrophages and mast cell induces fever
  3. As the blood vessel constricts along with an increase in metabolism and shivering the body temperature raises
  4. Elimination of Interleukin-1 (IL-1) will reduce body temperature to 37°C from 39°C
  5. Crisis of a fever
    - a. With a decrease in IL-1 vasodilation occurs
    - b. The thermostat is reset to 37°C resulting in the body perspiring as internal heat shed.
- B. Complications of fever (possible side affects)
1. Increase tachycardia (rapid heart rate) elderly people with cardiopulmonary disease are at increased risk
  2. Increased metabolic rate (may produce acidosis)
  3. Dehydration
  4. Electrolyte imbalances from dehydration
  5. Seizures in young children may result
  6. Delirium and possible coma.
- As a rule, death results if body temperature rises above 44-46°C or 112-114°F

## VII. Complement System

**What is the complement system? And it role in protecting the host?**

A group of 30 proteins found in the serum that can bind to antigens by themselves or with involvement of antibodies. The complement system role is to mediate inflammation and attract phagocytes and coat antigens. The coating of antigens is called **opsonization**.

**Antibodies** are proteins produced by lymphocytes that can specifically bind a wide variety of protein and polysaccharide antigens and elicit a response that is significant in antimicrobial defense. In conjunction with the complement system, antibodies are the mediators of humoral (circulating) immunity, and their presence on mucosal surfaces provides resistance to many infectious agents. Antibodies are essential for the prevention and/or cure of many types of bacterial and viral infections. As mediators of immunity, it was discovered at the turn of the century that antibodies were contained within the serum fraction of blood. It was demonstrated in 1939 that antibodies were specifically located in the gamma fraction of electrophoresed serum, thus the term **gammaglobulin** was coined for serum containing antibodies. Antibodies themselves, were called **immunoglobulins**.

1. Complement is an enzymatic system of serum proteins made up of 9 major components (C1 - C9).
  - a. Activated in many Ag - Ab reactions resulting in the disruption of membranes
  - b. Classical pathway
    - 1) Reaction between antibodies and antigens on surface of microbe
      - a) IgG and IgM involved
  - i. Cascade response: Generation of inflammatory factors
    - a) C2a and C5a - focus antimicrobial serum factors and leukocytes into the site of infection
  - ii. Attraction of phagocytes
    - a) Chemotactic factors C3a and C5a attract phagocytes to site
  - iii. Enhancement of phagocytic engulfment
    - a) C3b component of Ag - Ab complex attached to C3b receptors on phagocytes and promotes opsonization of Ab-coated cells. C3b-opsonization is important when Ab is IgM because phagocytes have receptors for Fc of IgM only when it is associated with C3b.
  - iv. Lysis of bacterial cells( lysozyme-mediated) or virus-infected cells.
    - a) When C8 and C9 are bound to the complex, a phospholipase is formed that destroys the membrane of AG-bearing host cells (virus infected cell) or the outer membrane of Gram-negative bacteria.
    - b) Lysozyme gains access to peptidoglycan and completes destruction of the bacterial cell.
2. Alternative pathway
  - a) Exists independent of immunoglobulins.
  - b) Insoluble polysaccharides (including bacterial LPS, peptidoglycan and teichoic acid) can activate complement.
  - c) Allows antibody-independent activation of complement cascade.

### 3. Lectin pathway

- a) Microbe exhibits mannose sugar markers that lectin protein binds to
- b) C2 and C4 broken down into C2a and C4b respectively
  - 1) C2a and C4b combined to make C3 convertase enzyme that cleaves C3 into C3a and C3b initiating cascade response.

### What are cytokines?

**Cytokines** and **lymphokines** are molecules (peptides, proteins) produced by cells as a means of intercellular communication. Generally, they are secreted by a cell to stimulate the activity of another cell. Cytokines and lymphokines include modulators called interleukins and interferons involved in the regulation of the immune cells.

### VIII. Interferons

#### A. Three class of interferons

1. Alpha interferon (IFN- $\alpha$ )
  - a. secreted in small amounts by infected monocytes, macrophages and some lymphocytes.
2. Beta Interferon (IFN- $\beta$ )
  - a. secreted in small amounts by undifferentiated cells in connective tissues (cartilage, tendons, and bone)
3. Gamma interferon (IFN- $\gamma$ )
  - a. Secreted by T-lymphocytes and NK lymphocytes later in the infection cycle
    - 1) Stimulates the activity of macrophages: *Macrophage activation factor*

#### B. Mode of Action

1. IFN- $\alpha$  and IFN- $\beta$  have similar modes of action within eukaryotic cells
2. Cells that secrete these biochemical factors are not protected by IFN
  - a. Rather, IFN from infected cells trigger activation of NK lymphocyte and protective responses in neighboring uninfected cells.
    - 1) Protective responses in neighboring uninfected cells
      - a) Production of antiviral proteins (two types of AVPs) that bind to viral nucleic acid particles preventing their expression.
        - 1) oligoadenylate synthetase: degrades mRNA
        - 2) protein kinase: inhibits protein synthesis at mRNA level
        - 3) both proteins work for 3 to 4 days.
3. (IFN- $\gamma$ )
  - a. Secreted by T-lymphocytes and NK lymphocytes later in the infection cycle
    - 1) Stimulates the activity of macrophages: *Macrophage activation factor*

Table: Antimicrobial substance of host origin present in body fluids and tissues

Substance	Common Sources	Chemical composition	Activity
Lysozyme	Serum, saliva, sweat, tears	Protein	Bacterial cell lysis
Complement	Serum	Protein-carbohydrate lipoprotein complex	Cell death or lysis of bacteria; participates in inflammation
Basic proteins and polypeptides (histones, $\beta$ -lysins and other cationic proteins, tissue polypeptides)	Serum or organized tissues	Proteins or basic peptides	Disruption of bacterial plasma membrane
Lactoferrin and transferrin	Body secretions, serum, organized tissue spaces	Glycoprotein	Inhibit microbial growth by binding (withholding) iron
Peroxidase	Saliva, tissues, cells (neutrophils)	Protein	Act with peroxide to cause lethal oxidation of cells
Fibronectin	Serum and mucosal surfaces	Glycoprotein	Clearance of bacteria (opsonization)
Interferons	Virus-infected cells, lymphocytes	Protein	Resistance to virus infections
Interleukins	Macrophages, lymphocytes	Protein	Cause fever, promote activation of immune system