WHY IS THIS IMPORTANT?

- Innate immune responses are nonspecific host defense mechanisms.
- They are of paramount importance for fighting off infectious disease.

OVERVIEW
TWO TYPES OF IMMUNE RESPONSE

- Innate
  - Nonspecific, immediately available, without memory
- Adaptive
  - Specific, takes several days to develop, has memory

INNATE IMMUNE RESPONSE

- Has two parts:
  - Barriers - prevent the entry of pathogens
  - Cellular and chemical mechanisms - destroy pathogens
- Responses are triggered by damage to cells or tissues.

FIRST LINE OF DEFENSE: Barriers

- Natural barriers are the first line of defense.
  - Not exclusively defense mechanisms and have other functions
- Two types of barriers:
  - Mechanical
    - Skin
    - Mucous membranes
  - Other barriers – lachrymal apparatus, saliva, and epiglottis
  - Chemical
MECHANICAL BARRIERS: Skin

- Skin is covered in microorganisms.
- It is impermeable to entry by microorganisms.
  - Entry requires breaks in the skin.

- Skin is divided into two layers:
  - Epidermis – no access to blood so only localized infection occurs
  - Dermis – access to blood vessels so infection here can become systemic
- Loss of skin can lead to serious infection.
  - Burn injuries

MECHANICAL BARRIERS: Mucous Membranes

- Found in systems with access to the outside of the body
  - Respiratory tract
  - Gastrointestinal tract
  - Genitourinary tract
- Primary function is to keep tissues moist.
- They can also trap microorganisms in mucus.
  - The mucociliary escalator of the respiratory tract
MECHANICAL BARRIERS: Mucous Membranes

- Protects the eyes from entry by pathogens.
  - Causes tears to flush across eye
  - Tears contain lysozyme, lipocalin, and IgA

MECHANICAL BARRIERS: Lachrymal Apparatus

- Protects the eyes from entry by pathogens.
  - Causes tears to flush across eye
  - Tears contain lysozyme, lipocalin, and IgA

MECHANICAL BARRIERS: Saliva

- Cleans teeth and tissues of the oral cavity
- Prepares food for digestion
- Inhibits microbial growth:
  - Contains lysozyme and IgA
MECHANICAL BARRIERS:
Epiglottis

- Prevents aspiration of food into the lungs.
- Also prevents entry of microorganisms into the lungs.

CHEMICAL BARRIERS

- Many chemical substances are secreted by the body including:
  - Sebum
  - Perspiration
  - Gastric juice
  - Urine
  - Transferrin
- Barrier defense is not their primary function.

CHEMICAL BARRIERS:
Sebum

- Produced by sebaceous glands
  - Forms a protective layer on the skin.
- Contains unsaturated fatty acids and organic acids
  - Inhibit bacterial growth by lowering pH.
CHEMICAL BARRIERS: Perspiration

- Regulates body temperature and eliminates waste
- Barrier against microorganisms in two ways:
  - Flushes them from the skin
  - Contains lysozyme

CHEMICAL BARRIERS: Gastric Juice

- Gastric juice includes:
  - Stomach acids
  - Enzymes
- The harsh chemical environment limits microbial growth.
- Some organisms survive this environment
  - *Helicobacter pylori* resides in the stomach.

CHEMICAL BARRIERS: Urine

- Used to secrete waste material from the body
- Barrier against microorganisms in two ways:
  - It is acidic.
  - Its flushing action prevents attachment
CHEMICAL BARRIERS:
Transferrin

- Transferrin binds iron.
- It competitively inhibits the growth of pathogens.

SECOND LINE OF DEFENSE:
Cellular and Chemical Responses

- One cellular response:
  - Phagocytosis
- Several chemical responses:
  - Inflammation
  - Fever
  - The complement system
  - Interferon

TOLL-LIKE RECEPTORS

- Toll-like receptors (TLRs) are used to differentiate between self and nonself antigens.
  - Located on the surface of host defense cells
  - Bind to antigens found on pathogens
TOLL-LIKE RECEPTORS

- TLRs are activated as soon as it binds to a target antigen.
- Causes the host cell to release inflammatory substances
  - Primarily tumor necrosis factor (TNF)

TOLL-LIKE RECEPTORS

<table>
<thead>
<tr>
<th>TOLL-like Receptor</th>
<th>Ligand Bound</th>
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<tr>
<td>TLR-1</td>
<td>Lipoproteins</td>
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<td>TLR-2</td>
<td>Bacterial lipoproteins</td>
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<td>Double-stranded RNA</td>
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<td>Lipopolysaccharide, some viral proteins</td>
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<td>Flagellar protein</td>
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<tr>
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<td>Lipopolysaccharide acid</td>
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<td>Single-stranded RNA</td>
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<td>TLR-13</td>
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</tbody>
</table>

CELLULAR RESPONSE:
Phagocytosis

- The innate immune response relies on white blood cells
  - Derived from bone marrow stem cells
  - Numbers correlate with stages of infection.
  - Identified by a complete blood count and differential blood test.
CELLULAR RESPONSE: Phagocytosis

- 2 types of white blood cell:
  - Granulocytes
  - Agranulocytes

- Granulocytes
  - Have granular cytoplasm and multilobed nuclei
  - There are three types:
    - Neutrophils
    - Basophils
    - Eosinophils
**CELLULAR RESPONSE: Phagocytosis**

- Neutrophils: Phagocytic cells
  - Guard skin and mucous membranes
  - Make up about 70% of white blood cell population
  - Derived from bone marrow and mature there
  - Use TLRs to detect components of pathogens.

- Circulate in the blood for 6 to 10 hours
  - Remain in tissues for up to 2-6 days
  - Guided to site of tissue damage by chemotaxis

**CELLULAR RESPONSE: Granulocytes**

- Neutrophils
  - Use margination to stop at the site of infection
  - Passage from blood into tissues is called diapedesis
  - Neutrophil function is tightly controlled
    - Have a short life span
    - Are programmed for apoptosis
CELLULAR RESPONSE: Granulocytes

- Basophils
  - Derived from progenitor cells in the bone marrow
  - Have a short life span – only a few days
  - Only small numbers circulate in blood

- Activated by bacteria, viruses, and parasites (using TLRs)
- They carry receptors for IgE
- The binding of IgE causes the release of histamine
  - Histamine amplifies innate immune reactions.

- Eosinophils
  - Very small numbers circulate in the blood
    - Numbers increase in cases of parasitic infection and allergic response
  - Primary defense to parasite infection
    - Produce powerful enzymes that attack parasites
  - Eosinophils can modulate the inflammatory response
CELLULAR RESPONSE: Granulocytes

- Have cytoplasmic granules that are not easily seen
- Three types of agranulocytes:
  - Monocytes
  - Macrophages
  - Lymphocytes – part of the adaptive immune system

CELLULAR RESPONSE: Agranulocytes

- Monocytes
  - Derived from bone marrow cells
  - Only small numbers circulate in the blood:
    - Circulate in a nonphagocytic form
    - Numbers increase during infection.
CELLULAR RESPONSE: Agranulocytes

- **Monocytes**
  - Guided to the site of tissue damage by chemotaxis:
    - Second cell type to arrive at the site of infection.
    - Differentiate into powerful phagocytic macrophages at the site.

- **Macrophages**
  - Responsible for the phagocytosis of:
    - Bacteria
    - Fungi
    - Parasites.
  - Also attack tumor cells and normal cells that are functioning abnormally.

- **Macrophages**
  - Remove cellular debris
  - Three types of macrophage:
    - Derived from monocytes
    - Wandering – move throughout the body
    - Resident (fixed) – stay in specific locations.
  - Part of the mononuclear phagocytic system.
CHEMICAL MEDIATORS: Cytokines and Chemokines

- Two types of chemical mediators of the innate immune response:
  - Cytokines
  - Chemokines
- They are both produced at the onset of and throughout the infection.

CHEMICAL MEDIATORS: Cytokines

- Low molecular weight proteins
- Released by a variety of cell types
  - Release is in response to stimuli associated with infection.
- Induce innate immune responses
- Affect the cells that produce them and other cells
CHEMICAL MEDIATORS: Cytokines

- Two families of cytokines:
  - Hematopoietin family
  - Tumor necrosis family
- Both involved in innate and adaptive immune response.

CHEMICAL MEDIATORS: Cytokines

- All cytokines have the same defining characteristics:
  - Secreted from white blood cells
  - Regulate inflammatory and immune responses
  - React with specific receptors on target cells
    - Alter activity of those cells
  - Have overlapping functions
    - Induce or inhibit effects of other cytokines
  - Activity is concentration dependent
CHEMICAL MEDIATORS:
Cytokines

- Cytokines that appear at the earliest time during infection:
  - Attract defensive cells to the site of infection
  - Released by many types of immune cells
  - Some are involved in angiogenesis and tissue repair.

CHEMICAL MEDIATORS:
Chemokines

- Two broad groups:
  - CC Group
  - CXC Group

- The CC group
  - Promote migration of monocytes and lymphocytes
  - Induce monocytes to differentiate into macrophages
CHEMICAL MEDIATORS: Chemokines

- The CXC group
  - Promote migration of neutrophils to the site of infection
  - Promote diapedesis

Both groups are released in response to:
- Bacterial or viral infection
- Tissue damage
- Chemokines also play a role in the destruction of pathogens.

OTHER CELLS IMPORTANT IN THE INNATE IMMUNE RESPONSE

- Three other types of cell are very important in the innate immune response:
  - Mast cells
  - Dendritic cells
  - Natural killer cells
MAST CELLS

- Derived from bone marrow stem cells
- Also known as sentinel cells
- Responsible for allergic responses and parasitic infections
- Found throughout the body
  - Mostly in tissues exposed to the external environment

MAST CELLS

- Have three distinct properties:
  - Rapid and selective production of mediators
  - Enhancement or recruitment of effector cells
  - Influence the adaptive immune response

MAST CELLS

- Leave the bone marrow in an immature form
  - Mature when they arrive at tissues sites
  - Use TLRs to identify pathogens
  - Activated by invading pathogens
**MAST CELLS**

- Produce a variety of mediators
  - Cause alterations in vascular function and cellular recruitment
- Can reposition during tissue repair
- Can initiate and maintain the adaptive immune response
- Work in concert with the complement system

**MAST CELLS**

- The mast cell response can damage the host.
  - Due to the proximity of the blood vessels
  - Can cause vasculitis and atherosclerosis

**DENDRITIC CELLS**

- Regulate both the innate and adaptive immune response
- Have long membranous extensions
- Produced continually in the bone marrow
DENDRITIC CELLS

- Have a strategic location in mucosal tissues
  - Associated with routes of pathogen entry
  - Effects depend on location

DENDRITIC CELLS: Skin and Mucous Membranes

- Dendritic cells in the skin are called Langerhans cells
  - Located in basal layers of the epidermis
  - Connected to each other forming a network
  - Renewed by progenitor cells in the skin

- Activated by the capture of antigen
  - After activation, they move to regional lymph nodes.
  - This can trigger the adaptive immune response.
- Have the same function in skin and mucous membranes
  - Replaced by bone marrow-derived cells in mucous membranes
- In mucous membranes, cells are replaced by bone marrow-derived cells.
DENDRITIC CELLS: 
Intestines

- Found in two locations:
  - Peyer’s patches
  - Lamina propria
- Can extrude dendrites through tight junctions into the intestinal lumen

DENDRITIC CELLS: 
Lymphoid Tissues

- Dendritic cells in the lymphoid tissues are mature but less phagocytic.
  - Produce the inflammatory cytokines and chemokines
  - Use TLRs to identify nonself antigens
  - Bind antigens and move to areas of the lymph node where the T cells are located

NATURAL KILLER CELLS

- Found in peripheral tissues and blood
  - Different types found in different tissues
- Derived from bone marrow stem cells
  - Use margination and diapedesis to leave the blood
NATURAL KILLER CELLS

- Do not use TLRs for identification of pathogens
  - Kill tumor cells, virus infected cells, bacteria, fungi, and parasites
- Response is diminished in HIV infection

NATURAL KILLER CELLS

- Involved in the innate response in two ways:
  - Kill target cells
  - Produce cytokines
- Target cell killing is:
  - Mediated by apoptosis of the target cell
  - Triggered by the release of perforin and granzymes

NATURAL KILLER CELLS

- Produce a variety of cytokines:
  - TNF
  - Granulocyte-macrophage colony stimulating factor
- Also respond to cytokines
NATURAL KILLER CELLS

PHAGOCYTOSIS

- Phagocytosis is the cellular mechanism of the innate response.
- It is primarily carried out by:
  - Neutrophils
  - Macrophages
- Both are attracted to site of tissue destruction by chemotaxis.
  - Neutrophils arrive first.
  - Then monocytes – differentiate into macrophages as they arrive.

PHAGOCYTOSIS

- Phagocytosis has five phases:
  - Chemotaxis
  - Adherence
  - Ingestion
  - Digestion
  - Excretion
PHAGOCYTOSIS

FIVE PHASES OF PHAGOCYTOSIS:

Chemotaxis

- Chemicals are released from damaged tissue.
- These chemicals attract phagocytic cells.
  - Move down the gradient to the site of damage

Adherence

- The plasma membrane of the phagocytic cell makes contact with pathogen.
- Some bacteria can inhibit this step.
FIVE PHASES OF PHAGOCYTOSIS: Ingestion

- The pathogen is taken into a phagocytic cell.
  - Pseudopodia envelop the pathogen.
  - A vesicle forms around the pathogen – a phagosome.

FIVE PHASES OF PHAGOCYTOSIS: Digestion

- The phagosome fuses with a lysosome in the phagocytic cell.
  - This forms a phagolysosome.
- Enzymes from the lysosome destroy the pathogen.
  - This can take as little as 30 minutes.
**FIVE PHASES OF PHAGOCYTOSIS:**

**Excretion**

- After digestion, phagolysosomes contain pathogen fragments.
  - Residual bodies
  - These move to the surface of the phagocyte and discharge debris.

**DEFEATING PHAGOCYTOSIS**

- Some bacteria can resist phagocytosis.
  - Produce enzymes to destroy phagocytic cells
  - Produce capsules that inhibit adherence
  - Resist digestion
  - Destroy the phagolysosome membrane

**DEFICIENCY IN PHAGOCYTOSIS**

- Some patients can be deficient in phagocytosis
  - Chemotherapy and/or radiation patients
  - Immunocompromised patients
  - Transplant patients
INFLAMMATION

* The normal physiological response to trauma
  * Helps destroy pathogens
  * Involved in tissue repair and replacement

INFLAMMATION

* Four symptoms – all related to vasodilation:
  * Redness
  * Pain
  * Heat
  * Swelling

INFLAMMATION: Vasodilation

* Vasodilation is the cornerstone of inflammation.
  * Involves localized reactions
  * Characterized by increased blood flow
* The injured area becomes redder and warmer.
* Surrounding areas become swollen by fluid from blood vessels.
  * Swelling puts pressure on local pain receptors.
**INFLAMMATION: Vasodilation**

- Occurs in response to the release of chemical signals
- Four major chemical signals:
  - Histamine – found in many cell types
    - Enhances vasodilation
  - Kinins – released from damaged tissue
    - Recruit more phagocytic cells

- Prostaglandins – intensify effects of histamine and kinins
  - Help migration of phagocytes out of the blood and into tissues
- Leukotrienes – produced by mast cells
  - Promote adherence of phagocytic cells

- Also delivers clotting elements
  - These can wall off the affected area.
  - This can prevent the spread of infection.
**INFLAMMATION: Phagocytic Migration**

- Vasodilation leads to increased numbers of defensive cells.
- They must stop and leave the blood at the site of the trauma.
  - Stick to blood vessel walls – margination
  - Leave and move into tissue – diapedesis

**THE ACUTE PHASE RESPONSE**

- Only seen in acute illness
- Acute-phase proteins are produced:
  - Cytokines
    - IL-6 – causes production of more acute-phase proteins
  - Fibrinogen
    - Used in clotting
  - Kinins
    - Increase vasodilation

**THE ACUTE PHASE RESPONSE**

- Best known acute-phase proteins are:
  - C-reactive protein
    - Binds to phospholipids
  - Mannose-binding protein
    - Binds to mannose sugars on bacterial and fungal membranes
    - Coating attracts phagocytic cells
    - Also activates the complement system
FEVER

- Fever is a systemic rise in body temperature.
  - Clinically – oral temperature above 37.8°C, rectal above 38.4°C.
  - Often accompanies and augments inflammation
  - Can accompany certain immune responses
    - Most types of tissue injury cause fever

FEVER

- Caused by two types of pyrogen:
  - Exogenous – produced by invading pathogens
  - Endogenous – produced by the host
    - Interleukin-1 (IL-1)

FEVER

- IL-1 moves to hypothalamus
  - Causes release of prostaglandin
  - Fever continues as long as IL-1 is present
  - Crisis phase – when fever diminishes
FEVER

- Fever is a good thing.
  - It increases the speed of host defenses.
  - It causes the patient to rest.

FEVER

- Unchecked fever can be dangerous.
  - Causes denaturation of proteins
  - Inhibits CNS function
  - Causes dehydration and electrolyte imbalance
  - In extreme cases it can lead to coma
- Antipyretics are used to prevent temperature from rising too high.

THE COMPLEMENT SYSTEM

- The complement system has a lethal capability.
  - It also amplifies other innate responses.
  - It is activated immediately upon invasion by pathogens.
THE COMPLEMENT SYSTEM

- About 30 serum proteins are involved
  - They are produced in the liver and circulate in an inactive form.
  - Some function in a cascade sequence.
  - Those not involved in the cascade manage the regulation of the cascade.

Major function is lysis of the bacterial cell wall or viral envelope.
- Accomplished through the membrane attack complex
THE COMPLEMENT SYSTEM

- Interactions between complement proteins can follow three pathways:
  - Classical
  - Alternative
  - Lectin-binding

ACTIVATION OF THE CLASSICAL PATHWAY

- The classical pathway is seen in infections that have been seen before.
  - It is activated by antibody-antigen complexes.
  - Complement cascade proteins are numbered C1 through C9.
ACTIVATION OF THE ALTERNATIVE PATHWAY

- The alternative pathway works with pathogens that have never seen before.
- It is activated by three factors:
  - Factor B
  - Factor D
  - Factor P – properdin (also known as the properdin pathway)
  - They interact with LPS and endotoxin from the pathogen.
  - Complement protein C3 is attracted to this complex.

ACTIVATION OF THE ALTERNATIVE PATHWAY

- The alternative pathway is less efficient than the classical pathway.
  - It is still very useful in the early stages of infection.

ACTIVATION OF THE ALTERNATIVE PATHWAY

- [Diagram showing the activation process of the alternative pathway]
ACTIVATION OF THE LECTIN-BINING PATHWAY

- The lectin-binding pathway is stimulated by mannose.
  - It involves mannose-binding proteins.
  - They enzymatically cleave the complement protein C3.

C3 AND BEYOND

- All three pathways lead to C3.
  - C3 is the nexus of complement.
- Complement proteins C3 through C9:
  - Cause lysis
  - Amplify inflammation.
- Complement proteins C5 through C9 are the membrane attack complex.
C3 AND BEYOND

- Pathogens have defenses against complement.
  - Encapsulation
    - Discourages formation of membrane attack complex
  - Some Gram-negative bacteria lengthen surface glycolipids.
    - Prevents membrane attack
  - Some Gram-positive bacteria release enzymes.
    - Limit amplification of innate responses by complement.

COMPLEMENT DEFICIENCIES

- Some people are genetically deficient for complement components.
  - They are more prone to infections.
  - C3 deficiencies are the most dangerous.
**INTERFERON**

- Production of interferon is a host response to viral infection.
- Produced by and released from virus-infected cells
  - Moves to uninfected neighboring cells
  - Causes them to produce antiviral proteins
  - Makes uninfected cells resistant to infection

**INTERFERON**

- Different types are produced by different types of cells.
- There are three major forms:
  - Alpha – produced by monocytes and macrophages
  - Beta – produced by fibroblasts
    - Both are produced immediately after infection by viruses
  - Gamma – produced by T cells and Natural Killer cells
    - Protect against viral infection
    - Also re-stimulates macrophage activity

**INTERFERON**

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<th>Class</th>
<th>Cell Source</th>
<th>Stimulated By</th>
<th>Effects</th>
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</thead>
<tbody>
<tr>
<td>Alpha interferon (IFN-α)</td>
<td>Leukocytes</td>
<td>Virus infection</td>
<td>Stimulates production of antiviral proteins in uninfected cells</td>
</tr>
<tr>
<td>Beta interferon (IFN-β)</td>
<td>Fibroblasts</td>
<td>Virus infection</td>
<td>Same as those seen with IFN-α</td>
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<tr>
<td>Gamma interferon (IFN-γ)</td>
<td>T lymphocytes and natural killer cells</td>
<td>Virus infection and antigenic stimulation</td>
<td>Kills infected cells and activates destruction of tumors</td>
</tr>
</tbody>
</table>

Table 9.3.1: Microbiology: A Clinical Approach © Garland Science
Some people are genetically predisposed to infection:
- Genetic deficiency in TLRs
- Inability to produce cytokines or chemokines
- Deficiency in complement proteins
- Genetic deficiency in interferon production