The Innate Immune Response
FUNCTIONS OF THE IMMUNE SYSTEM:

• Recognize, destroy and clear a diversity of pathogens.
• Initiate tissue and wound healing processes.
• Recognize and clear damaged self components.

Exhibit “tolerance” to innocuous material including self
The Normal Immune Response

The normal immune response is best understood in the context of defense against infectious pathogens, the classical definition of immunity.

Innate immunity refers to defense mechanisms that have evolved to specifically recognize microbes and protect individuals against infections.

Adaptive immunity consists of mechanisms that are stimulated and are capable of recognizing microbial and nonmicrobial substances.
**Innate immunity**
The first line of defense always ready to prevent and eradicate infections.

**Adaptive immunity**
Develops later, after exposure to microbes, and is even more powerful than innate immunity in combating infections.

By convention, the term “immune response” refers to adaptive immunity.
Innate and Adaptive immunity represent two different arms of the immune system that work together in host defense.

Innate Immunity (natural/native):
- Provides immediate protection from infection.
- Is broadly specific to microbes and tissue damage products.
- Does not change in response to reinfection (non-adaptive)
- Initiates processes that lead to activation of adaptive immune responses.

Adaptive Immunity (specific/acquired):
- Appears to adapt to a variety of non-self components (acquired)
- Is highly specific to a particular molecule “antigen”
- Responses upon reinfection are faster, better and stronger (memory)
- Generates proteins and cells that enhance innate immune function.
INNATE IMMUNITY

A major components of innate immunity are epithelial barriers that block entry of microbes.

Epithelia of the skin and gastrointestinal and respiratory tracts provide mechanical barriers to the entry of microbes from the external environment.

Epithelial cells also produce anti-microbial molecules such as defensins, and lymphocytes located in the epithelia combat microbes at these sites.

If microbes do breach epithelial boundaries, other defense mechanisms are called in.
Skin

Chemical barrier (AMPs)

Immunological barrier

T cells  Eos  LC/DC  Mast cells  NK cells

Neut cells

Layers of the Epidermis

Epidermis - Stratum corneum - Stratum lucidum - Stratum granulosum - Stratum spinosum - Stratum germinativum

Dermis

Microbiome barrier  TJ complex  SC  SG  SS  SB

Physical barrier

http://ars.els-cdn.com/content/image/1-s2.0-S0091674912035634-gr1.jpg

http://www.bbcm.univ.trieste.it/~antimic/images/ampmech.jpg

AMPs are Multimodal & Multifunctional

- Stimulate innate and adaptive immune responses
- Cause autolytic enzyme release
- Block cell envelope synthesis
- Are attracted to the anionic microbial surface
- Assemble on the surface
- Translocate
- Permeabilize/damage the membrane (pores, channels)
- Block internal metabolic processes

http://4.bp.blogspot.com/-IIBlt5vn9Js/UKEWssuUTMI/AAAAAAAAByU/tSRUZjiBwxc/s1600/SKIN+LAYERS.jpg
Table 2

Properties of selected human antimicrobial peptides with known 3D structure.1

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1 Obtained from the Antimicrobial Peptide Database (http://apsm.stm.edc.edu/αP) [8]. Peptide hydrophobic amino acid content (percent) is represented by pho% in the table. Protein-binding potential [1] was re-named as Boman index in the APD database in 2003.
Defensins are antimicrobial peptides

http://www.nature.com/nri/journal/v9/n11/images/nri2655-f3.jpg
The two most important cellular reactions of innate immunity

*Inflammation*, the process in which phagocytic leukocytes are recruited and activated to kill microbes.

*Anti-viral defense*, mediated by dendritic cells and NK cells.
Steps of the Inflammatory Response

The inflammatory response is a body's second line of defense against invasion by pathogens. Why is it important that clotting factors from the circulatory system have access to the injured area?

1. Damaged tissues release histamines, increasing blood flow to the area.

2. Histamines cause capillaries to leak, releasing phagocytes and clotting factors into the wound.

3. Phagocytes engulf bacteria, dead cells, and cellular debris.

4. Platelets move out of the capillary to seal the wounded area.
Cells of the Immune System

Stem Cell

Lymphoid Stem Cell
- Lymphocytes
  - B Cell Progenitor
  - T Cell Progenitor
    - Natural Killer Cell
    - Tc Cell
    - Th Cell
  - Memory Cell
- Plasma Cell

Myeloid Progenitor
- Granulocytes
  - Neutrophil
  - Eosinophil
  - Basophil
  - Mast Cell
  - Monocyte
- Dendritic Cell
- Macrophage
Smear of peripheral blood

- erythrocyte
- lymphocyte
- neutrophil
- eosinophil
- basophil
- monocyte
- platelets
Innate vs Adaptive Immune Components

There are also humoral vs cellular immune components
<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Ranges</th>
</tr>
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</table>
| **Red blood cell count**      | **Male:** 4.32-5.72 trillion cells/L*  
                                | (4.32-5.72 million cells/mcL**)  
                                | **Female:** 3.90-5.03 trillion cells/L    
                                | (3.90-5.03 million cells/mcL)  |
| **Hemoglobin**                | **Male:** 13.5-17.5 grams/dL***  
                                | (135-175 grams/L)  
                                | **Female:** 12.0-15.5 grams/dL  
                                | (120-155 grams/L)  |
| **Hematocrit**                | **Male:** 38.8-50.0 percent  
                                | **Female:** 34.9-44.5 percent |
| **White blood cell count**    | **3.5-10.5 billion cells/L**  
                                | (3,500 to 10,500 cells/mcL)  |
| **Platelet count**            | **150-450 billion/L**  
                                | (150,000 to 450,000/mmol****) |

http://www.mayoclinic.com/health/complete-blood-count/MY00476/DSECTION=results
• **Granulocytes** (or polymorphonuclears)
  • **Neutrophils** (or segs): **50 - 70% relative value** (2500-7000 absolute value)
  • **Eosinophils**: 1 - 3% relative value (100-300 absolute value)
  • **Basophils**: 0.4% - 1% relative value (40-100 absolute value)

• **Agranulocytes** (or mononuclears)
  • **Lymphocytes**: **25 - 35% relative value** (1700-3500 absolute value)
  • **Monocytes**: 4 - 6% relative value (200-600 absolute value)

Each **differential** always adds up to 100%.

To make an accurate assessment, consider both relative and absolute values. For example a relative value of 70% neutrophils may seem within normal limits; however, if the total WBC is 20,000, the absolute value (70% x 20,000) would be an abnormally high count of 14,000.

Leukocytes and epithelial cells that participate in innate immunity are capable of recognizing components of microbes that are shared among related microbes and are often essential for the infectivity of these pathogens.
Recognition of PAMPs from different classes of microbial pathogens.

<table>
<thead>
<tr>
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<th>Gram-negative bacteria</th>
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<td>DNA sensors:</td>
<td>+</td>
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</table>

How are Things Recognized

These microbial structures are called pathogen associated molecular patterns (PAMPs).

Leukocytes also recognize molecules released by injured and necrotic cells, which are sometimes called danger-associated molecular patterns (DAMPs).

The cellular receptors that recognize these molecules are often called pattern recognition receptors.

The best-defined pattern recognition receptors are a family of proteins called Toll-like receptors (TLRs) that are homologous to the Drosophila protein Toll.
TLRs are specific for components of different bacteria and viruses. TLRs are located on the cell surface and in endosomes, so they are able to recognize and initiate cellular responses to extracellular and ingested microbes.

Upon recognition of microbes, the TLRs and other sensors signal by a common pathway that leads to the activation of transcription factors, notably NF-κB (nuclear factor κB). NF-κB turns on the production of cytokines and proteins that stimulate the microbicidal activities of various cells, notably the phagocytes.

Other cellular receptors bind microbes for phagocytosis; these include receptors for mannose residues, which are typical of microbial but not host glycoproteins, and receptors for opsonins such as antibodies and complement proteins that coat microbes.
Macrophages

Macrophages are a part of the mononuclear phagocyte system.

Macrophages that have phagocytized microbes and protein antigens process the antigens and present peptide fragments to T cells. Thus, macrophages function as APCs in T-cell activation.

Macrophages are key effector cells in certain forms of cell-mediated immunity, the reaction that serves to eliminate intracellular microbes. In this type of response, T cells activate macrophages and enhance their ability to kill ingested microbes.

Macrophages also participate in the effector phase of humoral immunity. Macrophages efficiently phagocytose and destroy microbes that are opsonized (coated) by IgG or C3b.
Monocytes and neutrophils are phagocytes in the blood that can rapidly be recruited to any site of infection; monocytes that enter the tissues and mature are called macrophages.
Endocytosis

Phagocytosis
- Solid particle
- Plasma membrane
- Pseudopodium
- Phagosome (food vacuole)

Pinocytosis
- Extracellular fluid
- Vesicle
- Cytoplasm

Receptor-mediated endocytosis
- Coated pit
- Receptor
- Coat protein
- Coated vesicle

http://php.med.unsw.edu.au/cellbiology/images/a/a8/Endocytosis_types.png
1. RECOGNITION AND ATTACHMENT
Microbes bind to phagocyte receptors

2. ENGULFMENT
Phagocyte membrane zips up around microbe

Microbe ingested in phagosome

3. KILLING AND DEGRADATION
Killing of microbes by ROIs and NO

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http://dc352.4shared.com/doc/-4JNWl_7/preview_html_m6a877314.jpg
Neutrophils are the first responders of the body's defense system.

Neutrophils rapidly localize to areas of acute infection and phagocytize bacteria. Their cytoplasmic granules contain proteases and they are capable of generating reactive oxygen intermediates to kill the invading organism.

Neutrophils are the most abundant white blood cell in circulation but they have a half life of only 1-2 days.
The proteins of the **complement system**, are some of the most important plasma proteins of the innate immune system.

In innate immunity the complement system is activated by microbes using the alternative and lectin pathways; in adaptive immunity it is activated by antibodies using the classical pathway.
Natural Killer Cells

NK cells are endowed with the ability to kill a variety of infected and tumor cells, without prior exposure to or activation by these microbes or tumors.

This ability makes NK cells an early line of defense against viral infections and, perhaps, some tumors.

CD16 is an Fc receptor for IgG, and it confers on NK cells the ability to lyse IgG-coated target cells. This phenomenon is known as *antibody-dependent cell-mediated cytotoxicity* (ADCC).

FIGURE 6–5A Activating and inhibitory receptors of natural killer (NK) cells. A, Healthy cells express self–class I MHC molecules, which are recognized by inhibitory receptors, thus ensuring that NK cells do not attack normal cells. Note that healthy cells may express ligands for activating receptors (not shown) or may not express such ligands (as shown), but they do not activate NK cells because they engage the inhibitory receptors.

FIGURE 6–5B Activating and inhibitory receptors of natural killer (NK) cells. A, Healthy cells express self–class I MHC molecules, which are recognized by inhibitory receptors, thus ensuring that NK cells do not attack normal cells. Note that healthy cells may express ligands for activating receptors (not shown) or may not express such ligands (as shown), but they do not activate NK cells because they engage the inhibitory receptors. B, In infected and stressed cells, class I MHC expression is reduced so that the inhibitory receptors are not engaged, and ligands for activating receptors are expressed. The result is that NK cells are activated and the infected cells are killed.

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The functional activity of NK cells is regulated by a balance between signals from activating and inhibitory receptors\textsuperscript{[10]}. There are many types of activating receptors, of which the NKG2D family is the best characterized. The NKG2D receptors recognize surface molecules that are induced by various kinds of stress, such as infection and DNA damage. NK cell inhibitory receptors recognize self–class I MHC molecules, which are expressed on all healthy cells.

The inhibitory receptors prevent NK cells from killing normal cells.

Virus infection or neoplastic transformation often induces expression of ligands for activating receptors and at the same time reduces the expression of class I MHC molecules.

As a result the balance is tilted toward activation, and the infected or tumor cell is killed.
MHC class I polypeptide-related sequence A (MICA)

Natural killer (NK) cells bear killer activation receptors (KARs) that detect stress-related molecules, MICA and MICB, and killer inhibition receptors (KIRs) that detect MHC class I molecules on nucleated cells in the body.
CD8+ T cell
NK cell

Mac
Mast
Neut
KC
Chond

Granzyme
Perforin

Inflammaging
Cleavage of IL-1α and extracellular matrix
Production of IL-6, IL-8, and GM-CSF
Loss of tissue structural integrity
Inflammation
Tissue injury and impaired tissue repair

Death of virus-infected cell
Major Histocompatibility Complex (MHC) Molecules: Peptide Display System of Adaptive Immunity

MHC molecules were discovered as products of genes that evoke rejection of transplanted organs, and their name derives from the recognition that they are responsible for tissue compatibility between individuals.

The physiologic function of MHC molecules is to display peptide fragments of proteins for recognition by antigen-specific T cells.

In humans the genes encoding the major histocompatibility molecules are clustered on a small segment of chromosome 6, the major histocompatibility complex, or the human leukocyte antigen (HLA) complex, so named because in humans MHC-encoded proteins were initially detected on leukocytes by the binding of antibodies. The HLA system is highly polymorphic, meaning that there are many alleles of each MHC gene in the population and each individual inherits one set of these alleles that is different from the alleles in most other individuals. This, as we see subsequently, constitutes a formidable barrier in organ transplantation.
FIGURE 6-8 The human leukocyte antigen (HLA) complex and the structure of HLA molecules. A, The location of genes in the HLA complex. The relative locations, sizes, and distances between genes are not to scale. Genes that encode several proteins involved in antigen processing (the TAP transporter, components of the proteasome, and HLA-DM) are located in the class II region (not shown). B, Schematic diagrams and crystal structures of class I and class II HLA molecules.

(Crystal structures are courtesy of Dr. P. Bjorkman, California Institute of Technology, Pasadena, CA.)
The innate immune system provides immediate protection. The adaptive response takes time to develop and is antigen specific.