The Immune System:
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Immunity: Two Intrinsic Defense Systems

- Innate (nonspecific) system responds quickly and consists of:
  - First line of defense – intact skin and mucosae prevent entry of microorganisms
  - Second line of defense – antimicrobial proteins, phagocytes, and other cells
    - Inhibit spread of invaders throughout the body
    - Inflammation is its hallmark and most important mechanism

Immunity: Two Intrinsic Defense Systems

- Adaptive (specific) defense system
  - Third line of defense – mounts attack against particular foreign substances
    - Takes longer to react than the innate system
    - Works in conjunction with the innate system

Surface Barriers

- Skin, mucous membranes, and their secretions make up the first line of defense
- Keratin in the skin:
  - Presents a formidable physical barrier to most microorganisms
  - Is resistant to weak acids and bases, bacterial enzymes, and toxins
- Mucosae provide similar mechanical barriers

Epithelial Chemical Barriers

- Epithelial membranes produce protective chemicals that destroy microorganisms
  - Skin acidity (pH of 3 to 5) inhibits bacterial growth
  - Sebum contains chemicals toxic to bacteria
  - Stomach mucosae secrete concentrated HCl and protein-digesting enzymes
  - Saliva and lacrimal fluid contain lysozyme

- Mucus traps microorganisms that enter the digestive and respiratory systems

Respiratory Tract Mucosae

- Mucus-coated hairs in the nose trap inhaled particles
- Mucosa of the upper respiratory tract is ciliated
  - Cilia sweep dust- and bacteria-laden mucus away from lower respiratory passages

Internal Defenses: Cells and Chemicals

- The body uses nonspecific cellular and chemical devices to protect itself
  - Phagocytes and natural killer (NK) cells
  - Antimicrobial proteins in blood and tissue fluid
  - Inflammatory response enlists macrophages, mast cells, WBCs, and chemicals
- Harmful substances are identified by surface carbohydrates unique to infectious organisms

Phagocytes

- Macrophages are the chief phagocytic cells
- Free macrophages wander throughout a region in search of cellular debris
- Kupffer cells (liver) and microglia (brain) are fixed macrophages
- Neutrophils become phagocytic when encountering infectious material
- Eosinophils are weakly phagocytic against parasitic worms
- Mast cells bind and ingest a wide range of bacteria

Mechanism of Phagocytosis

- Microbes adhere to the phagocyte
- Pseudopods engulf the particle (antigen) into a phagosome
- Phagosomes fuse with a lysosome to form a phagolysosome
- Invaders in the phagolysosome are digested by proteolytic enzymes
- Indigestible and residual material is removed by exocytosis

Mechanism of Phagocytosis

Natural Killer (NK) Cells

- Cells that can lyse and kill cancer cells and virus-infected cells
- Natural killer cells:
  - Are a small, distinct group of large granular lymphocytes
  - React nonspecifically and eliminate cancerous and virus-infected cells
  - Kill their target cells by releasing perforins and other cytolytic chemicals
  - Secrete potent chemicals that enhance the inflammatory response

Inflammation: Tissue Response to Injury

- The inflammatory response is triggered whenever body tissues are

injured
  - Prevents the spread of damaging agents to nearby tissues
  - Disposes of cell debris and pathogens
  - Sets the stage for repair processes
- The four cardinal signs of acute inflammation are redness, heat, swelling, and pain

Inflammation Response

- Begins with a flood of inflammatory chemicals released into the extracellular fluid
- Inflammatory mediators:
  - Include kinins, prostaglandins (PGs), complement, and cytokines
  - Are released by injured tissue, phagocytes, lymphocytes, and mast cells
  - Cause local small blood vessels to dilate, resulting in hyperemia

Toll-like Receptors (TLRs)

- Macrophages and cells lining the gastrointestinal and respiratory tracts bear TLRs
- TLRs recognize specific classes of infecting microbes
- Activated TLRs trigger the release of cytokines that promote inflammation

Inflammatory Response: Vascular Permeability

- Chemicals liberated by the inflammatory response increase the permeability of local capillaries
- Exudate (fluid containing proteins, clotting factors, and antibodies):
  - Seeps into tissue spaces causing local edema (swelling), which contributes to the sensation of pain

Inflammatory Response: Edema

- The surge of protein-rich fluids into tissue spaces (edema):
  - Helps to dilute harmful substances
  - Brings in large quantities of oxygen and nutrients needed for repair
  - Allows entry of clotting proteins, which prevents the spread of bacteria

Inflammatory Response: Phagocytic Mobilization

- Occurs in four main phases:
  - Leukocytosis – neutrophils are released from the bone marrow in response to leukocytosis-inducing factors released by injured cells
  - Margination – neutrophils cling to the walls of capillaries in the injured area

- Diapedesis – neutrophils squeeze through capillary walls and begin phagocytosis
- Chemotaxis – inflammatory chemicals attract neutrophils to the injury site

Inflammatory Response: Phagocytic Mobilization

Antimicrobial Proteins

- Enhance the innate defenses by:
  - Attacking microorganisms directly
  - Hindering microorganisms' ability to reproduce
- The most important antimicrobial proteins are:
  - Interferon
  - Complement proteins

Interferon (IFN)

- Genes that synthesize IFN are activated when a host cell is invaded by a virus
- Interferon molecules leave the infected cell and enter neighboring cells
- Interferon stimulates the neighboring cells to activate genes for PKR (an antiviral protein)
- PKR nonspecifically blocks viral reproduction in the neighboring cell

Interferon (IFN)

Interferon Family

- Interferons are a family of related proteins each with slightly different physiological effects
- Lymphocytes secrete gamma (γ) interferon, but most other WBCs secrete alpha (α) interferon
- Fibroblasts secrete beta (β) interferon
- Interferons also activate macrophages and mobilize NKs
- FDA-approved alpha IFN is used:
  - As an antiviral drug against hepatitis C virus
  - To treat genital warts caused by the herpes virus

Complement

- 20 or so proteins that circulate in the blood in an inactive form
- Proteins include C1 through C9, factors B, D, and P, and regulatory proteins
- Provides a major mechanism for destroying foreign substances in the body

Complement

- Amplifies all aspects of the inflammatory response
- Kills bacteria and certain other cell types (our cells are immune to complement)
- Enhances the effectiveness of both nonspecific and specific defenses

Complement Pathways

- Complement can be activated by two pathways: classical and alternative
- Classical pathway is linked to the immune system
  - Depends on the binding of antibodies to invading organisms
  - Subsequent binding of C1 to the antigen-antibody complexes (complement fixation)
- Alternative pathway is triggered by interaction among factors B, D, and P, and polysaccharide molecules present on microorganisms

Complement Pathways

- Each pathway involves a cascade in which complement proteins are activated in an orderly sequence and where each step catalyzes the next
- Both pathways converge on C3, which cleaves into C3a and C3b
- C3b initiates formation of a membrane attack complex (MAC)
- MAC causes cell lysis by interfering with a cell's ability to eject Ca^{2+}
- C3b also causes opsonization, and C3a causes inflammation

Complement Pathways
C-reactive Protein (CRP)

- CRP is produced by the liver in response to inflammatory molecules
- CRP is a clinical marker used to assess for:
  - The presence of an acute infection
  - An inflammatory condition and its response to treatment

Functions of C-reactive Protein

- Binds to PC receptor of pathogens and exposed self-antigens
- Plays a surveillance role in targeting damaged cells for disposal
- Activates complement

Fever

- Abnormally high body temperature in response to invading microorganisms
- The body's thermostat is reset upwards in response to pyrogens, chemicals secreted by leukocytes and macrophages exposed to bacteria and other foreign substances

Fever

- High fevers are dangerous as they can denature enzymes
- Moderate fever can be beneficial, as it causes:
  - The liver and spleen to sequester iron and zinc (needed by microorganisms)
  - An increase in the metabolic rate, which speeds up tissue repair

Adaptive (Specific) Defenses

- The adaptive immune system is a functional system that:
  - Recognizes specific foreign substances
  - Acts to immobilize, neutralize, or destroy foreign substances
  - Amplifies inflammatory response and activates complement

Adaptive Immune Defenses

- The adaptive immune system is antigen-specific, systemic, and has memory
- It has two separate but overlapping arms
  - Humoral, or antibody-mediated immunity
  - Cellular, or cell-mediated immunity

Antigens

- Substances that can mobilize the immune system and provoke an immune response
- The ultimate targets of all immune responses are mostly large, complex molecules not normally found in the body (nonself)

Complete Antigens

- Important functional properties:
  - Immunogenicity – the ability to stimulate proliferation of specific lymphocytes and antibody production
  - Reactivity – the ability to react with the products of the activated lymphocytes and the antibodies released in response to them
- Complete antigens include foreign protein, nucleic acid, some lipids, and large polysaccharides

Haptens (Incomplete Antigens)

- Small molecules, such as peptides, nucleotides, and many hormones, that are not immunogenic but are reactive when attached to protein carriers
- If they link up with the body's proteins, the adaptive immune system may recognize them as foreign and mount a harmful attack (allergy)
- Haptens are found in poison ivy, dander, some detergents, and cosmetics

Antigenic Determinants

- Only certain parts of an entire antigen are immunogenic
- Antibodies and activated lymphocytes bind to these antigenic determinants
- Most naturally occurring antigens have numerous antigenic determinants that:
  - Mobilize several different lymphocyte populations
  - Form different kinds of antibodies against it
- Large, chemically simple molecules (e.g., plastics) have little or no immunogenicity

Antigenic Determinants

Self-Antigens: MHC Proteins

- Our cells are dotted with protein molecules (self-antigens) that are not antigenic to us but are strongly antigenic to others
- One type of these, MHC proteins, mark a cell as self
- The two classes of MHC proteins are:
  - Class I MHC proteins – found on virtually all body cells
  - Class II MHC proteins – found on certain cells in the immune response

MHC Proteins

- Are coded for by genes of the major histocompatibility complex (MHC) and are unique to an individual
- Each MHC molecule has a deep groove that displays a peptide, which is a normal cellular product of protein recycling
- In infected cells, MHC proteins bind to fragments of foreign antigens, which play a crucial role in mobilizing the immune system

Cells of the Adaptive Immune System

- Two types of lymphocytes
  - B lymphocytes – oversee humoral immunity
  - T lymphocytes – non-antibody-producing cells that constitute the cell-mediated arm of immunity
- Antigen-presenting cells (APCs):
  - Do not respond to specific antigens
  - Play essential auxiliary roles in immunity

Lymphocytes

- Immature lymphocytes released from bone marrow are essentially identical
- Whether a lymphocyte matures into a B cell or a T cell depends on where in the body it becomes immunocompetent

- B cells mature in the bone marrow
- T cells mature in the thymus

T Cells

- T cells mature in the thymus under negative and positive selection pressures
  - Negative selection – eliminates T cells that are strongly anti-self
  - Positive selection – selects T cells with a weak response to self-antigens, which thus become both immunocompetent and self-tolerant

B Cells

- B cells become immunocompetent and self-tolerant in bone marrow
- Some self-reactive B cells are inactivated (anergy) while others are killed
- Other B cells undergo receptor editing in which there is a rearrangement of their receptors

Immunocompetent B or T cells

- Display a unique type of receptor that responds to a distinct antigen
- Become immunocompetent before they encounter antigens they may later attack
- Are exported to secondary lymphoid tissue where encounters with antigens occur
- Mature into fully functional antigen-activated cells upon binding with their recognized antigen
- It is genes, not antigens, that determine which foreign substances our immune system will recognize and resist

Antigen-Presenting Cells (APCs)

- Major rolls in immunity are:
  - To engulf foreign particles
  - To present fragments of antigens on their own surfaces, to be recognized by T cells
- Major APCs are dendritic cells (DCs), macrophages, and activated B cells
- The major initiators of adaptive immunity are DCs, which actively migrate to the lymph nodes and secondary lymphoid organs and present antigens to T and B cells

Macrophages and Dendritic Cells

- Secrete soluble proteins that activate T cells
- Activated T cells in turn release chemicals that:

- Rev up the maturation and mobilization of DCs
- Prod macrophages to become activated macrophages, which are insatiable phagocytes that secrete bactericidal chemicals

Adaptive Immunity: Summary

- Two-fisted defensive system that uses lymphocytes, APCs, and specific molecules to identify and destroy nonself particles
- Its response depends upon the ability of its cells to:
  - Recognize foreign substances (antigens) by binding to them
  - Communicate with one another so that the whole system mounts a response specific to those antigens

Humoral Immunity Response

- Antigen challenge – first encounter between an antigen and a naive immunocompetent cell
- Takes place in the spleen or other lymphoid organ
- If the lymphocyte is a B cell:
  - The challenging antigen provokes a humoral immune response
    - Antibodies are produced against the challenger

Clonal Selection

- Stimulated B cell growth forms clones bearing the same antigen-specific receptors
- A naive, immunocompetent B cell is activated when antigens bind to its surface receptors and cross-link adjacent receptors
- Antigen binding is followed by receptor-mediated endocytosis of the cross-linked antigen-receptor complexes
- These activating events, plus T cell interactions, trigger clonal selection

Clonal Selection

Fate of the Clones

- Most clone cells become antibody-secreting plasma cells
- Plasma cells secrete specific antibody at the rate of 2000 molecules per second

Fate of the Clones

- Secreted antibodies:
  - Bind to free antigens
  - Mark the antigens for destruction by specific or nonspecific mechanisms
- Clones that do not become plasma cells become memory cells that can mount an immediate response to subsequent exposures of the

same antigen

Immunological Memory

- Primary immune response – cellular differentiation and proliferation, which occurs on the first exposure to a specific antigen
  - Lag period: 3 to 6 days after antigen challenge
  - Peak levels of plasma antibody are achieved in 10 days
  - Antibody levels then decline

Immunological Memory

- Secondary immune response – re-exposure to the same antigen
  - Sensitized memory cells respond within hours
  - Antibody levels peak in 2 to 3 days at much higher levels than in the primary response
  - Antibodies bind with greater affinity, and their levels in the blood can remain high for weeks to months

Primary and Secondary Humoral Responses

Active Humoral Immunity

- B cells encounter antigens and produce antibodies against them
  - Naturally acquired – response to a bacterial or viral infection
  - Artificially acquired – response to a vaccine of dead or attenuated pathogens
- Vaccines – spare us the symptoms of disease, and their weakened antigens provide antigenic determinants that are immunogenic and reactive

Passive Humoral Immunity

- Differs from active immunity in the antibody source and the degree of protection
  - B cells are not challenged by antigens
  - Immunological memory does not occur
  - Protection ends when antigens naturally degrade in the body
- Naturally acquired – from the mother to her fetus via the placenta
- Artificially acquired – from the injection of serum, such as gamma globulin