

The Body's Defenses

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- The immune system is a security system that helps protect the animal's body from intruders, and is a recognition system that distinguished "self" from "non-self".

Nonspecific Defenses against Infection

- Nonspecific defense mechanism does not distinguish one infectious agent from another.

The skin and mucous membranes provide first-line barriers to infection

- The first line of the body's defense system consists of physical and chemical obstacles to the entry of intruders.
 - Skin: a toughened barrier.
 - Secretions:
 1. Secretions from sebaceous and sweat glands give the skin a pH of 3 ~ 5.
 2. **Lysozyme**, one of glycosidases presented in tears, saliva, and perspiration, can digest the cell walls of many bacteria.
 3. Gastric juice: pH < 2
 - **Mucus** coated the epithelium of the respiratory, digestive, and genitourinary tracts can trap microbes and other particles.

Phagocytic cells, inflammation, and antimicrobial protein function early in infection

- **Phagocytosis**: the second line, nonspecific internal mechanism of defense

Phagocytic and natural killer cells

- **Neutrophils** (PMNs): 60% ~ 70% of leukocytes, phagocytic

- **Chemotaxis:** chemical signal attraction and cell migration.
- **Macrophages** are developed from **monocytes**, 5% of leukocytes
 - More effective phagocytic defense
 - Free form and fixed form (alveolar macrophage in lungs, Kupffer's cell in liver, mesangial cells in kidney, microglial cells in brain, histiocytes in CNT, and macrophages in lymphatic tissues)
- **Eosinophils:** 1.5% of leukocytes, limited phagocytic activity
 - Against large parasitic invader: adhesion and enzyme releasing
- **Natural killer (NK) cells:** Cells attack on the membrane of the virus-infected cells and abnormal cells, not microorganisms, causing them to lyse.

The inflammatory response

- The most important element of inflammation – phagocytosis: endothelial cells or monocytes secreted **chemokines** attract neutrophils and macrophages
- Characterization of inflammatory
 - **Redness:** When injured, **basophils** and **mast cells** release **histamine** to dilate and increase permeability of nearby capillaries.
 - **Swelling:** Edema or leakiness of the capillaries enhances the cell migration.
 - **Heat (or fever):** resetting the body's thermostat to a higher temperature to inhibit growth of microorganisms.
 - Toxins produced by the pathogens or **pyrogens** release from WBCs
 - **Pain:** bradykinin-nerve

Antimicrobial proteins

- **Interferons** secreted by virus-infected cells can stimulate other cells to produce other chemicals to inhibit virus infection:
 - Interferon cannot save the infected cells.
 - The interferon is not virus-specific, but host-specific.

- **Complements:** A defense system cooperates with other mechanism.

How Specific Immunity Arises

Lymphocytes provide the specificity and diversity of the immune system

- **Specificity:** antigen and antibody binding.
 - **Antigen (Ag):** antibody-generating molecules
 - **Antibody (Ab):** proteins produced by activating **B lymphocytes**
 - Membrane-bound **antigen receptor:**
 - **T cell receptor (TCR)** in T lymphocytes:
 - Membrane antibodies as **B cell receptor (BCR)** in B lymphocytes:
- **Diversity:** During early development of each vertebrate, a type of genetic recombination creates an enormous variety of B and T cells in the body. Each cell bears antigen receptors of particular specificity. With the diversity of lymphocytes, the immune system has the capacity to respond to millions of different antigens, even ones that do not yet exist.

Antigens interact with specific lymphocytes, inducing immune responses and immunological memory

- **Clonal selection:** antigen-driven cloning of lymphocytes
 - Each lymphocyte recognizes and responds to only one antigenic **epitope**.
 - Each lymphocyte's specificity for an antigen is rigidly predetermined during embryonic development before encountering with the antigen.
 - Each antigen selectively activates a tiny fraction of cells from the body's diverse pool of lymphocytes.
 - Each selected lymphocyte is activated to divide and to differentiate forming two clones of cells: short-lived **effector cells** and long-live **memory cells**
 - Antibody-producing effector B cells: **plasma cells**

- **Primary immune response:** a lag period for lymphocytes selected by the antigen to proliferate and differentiate into effector B and T cells.
- **Secondary immune response:** more effective and prolonged
 - **Immunological memory:** More numerous antibody production and greater affinity for the antigen.

Lymphocyte development gives rise to an immune system that distinguishes self from nonself

- Lymphocytes: two distinct populations of lymphocytes, T cells and B cells.
 - **T cells:** lymphocytes migrate from bone marrow to the thymus where they are further mature (the T stands for **Thymus**).
 - **B cells:** lymphocytes remain in the bone marrow and continue their maturation (the B stands for **Bursa** of Fabricius of birds).

Immune tolerance for self

- Normally, there are no lymphocytes that are reactive against the body's own molecules--**self-tolerance:** any lymphocytes with receptors for molecules present in the body are destroyed or are rendered nonfunctional by **programmed cell death (apoptosis)** before birth.

The role of cell surface markers in T cell function and development

- **Major histocompatibility complex (MHC):** in humans, the MHC glycoproteins are also known as **HLA** (human leukocyte antigen)
 - **Antigen presentation:** A specific cell surface proteins can bind with antigen molecule.
 - **MHC I** molecules are found on all nucleated cells.
 - **MHC II** molecules are restricted to a few specialized cells: macrophages,

B cells, activated T cells, etc.

- A **bio-fingerprint** unique to each individual: Since there are at least 20 MHC genes and at least 50 alleles for each gene, it is virtually impossible for any two people to have matching sets of MHC markers on their cells unless the identical twins.

Immune Responses

- **Humoral immunity** is resulting in the production of antibodies.
- **Cell-mediated immunity** is carried out by highly specialized cells.

Helper T lymphocytes function in both humoral and cell-mediated immunity: an overview

- **Antigen-presenting cells (APCs)**: macrophages and B cells.
 - Macrophage can display a wide variety of antigens (taken in by phagocytosis), but each B cells can display only one type of antigen (bound to surface Ab and taken in by endocytosis).
- **MHC II** with digested antigen on **APC – CD4** on **helper T cell (T_H)**:
 - **Cytokine** secretion:
 - **Interleukin-I** secreted from macrophage stimulates T_H activation.
 - **Interleukin-II** secreted from T_H stimulates T_H, T_C and B cells activation.

In the cell-mediated response, cytotoxic T cells counter intracellular pathogens: a closer look

- **MHC I** with synthesized antigen on infected cells or tumor cells interacts with **CD8** on **cytotoxic T cells (T_C)**: **Perforin** forms an open lesion in the infected cell's plasma membrane that causes cell to lyse.

- Certain cancers and virus reduce the amount of MHC I on affected cells:

In the humoral response, B cells make antibodies against extracellular pathogens: a closer look

- **T-cell dependent activation:** Ag/APC - T_H - B → Ab

- Most protein antigens are T-dependent

- **T-cell independent activation:** some types of antigens like polysaccharides and proteins with many identical polypeptides directly stimulate B cells to form plasma cells without involving T_H and IL-2.

- The response to T-independent antigen is general much weaker than the response to T-dependent antigens, and no memory cells are generated.

- Very important in defending against many bacteria:

Antibody structure and function

- Most antigens are large molecules such as proteins or polysaccharides.

- One specific antibody does not recognize the whole molecule of antigen, but a localized region: **epitope** or **antigenic determinant**.

- An antibody (**immunoglobulin, Ig**) consists two identical **light (L) chains** and two identical **heavy (H) chains**, which are linked by -S-S- to formed Y-shape.

- Both H and L chains have **variable (V) regions**, and **constant (C) regions**.

- V regions at the end of the two arms of the Y are **Antigen-binding site**.

- There are five types of constant regions and hence five major classes of antibodies in mammals: **IgM, IgD, IgG, IgE, and IgA**. Each class plays a different role in the immune response.

- **Monoclonal Antibody** Technology: monoclonal - polyclonal

- **Hybridoma:** the fusion of spleen B cell and myeloma cell

Antibody-mediated disposal of antigen

- The main function of antibody is recognition and binding to a specific antigen: Antibodies do not destroy antigen-bearing invaders directly. Instead, they tag surface of foreign molecules or cells (**opsonization**) to facilitate phagocytosis by macrophage or destruction by complements.
- **Neutralization:** blocks the harmful parts of viruses and bacterial toxins.
- **Agglutination:** bacteria and other foreign cells
- **Precipitation:** the cross-linking of soluble antigen molecules (rather than cells) to form immobile precipitates.
- **Complement fixation** (activation of complement):
 - Complement consists of about 20 different serum proteins.
 - The complement proteins which inactive form circulating in the blood, is activated either by the onset of the immune response or by chemical markers on the surface of microorganisms to trigger a cascade reaction.
 - **Membrane attack complex (MAC):** inserting into the membrane of pathogen to cause lysis.
 - **Classical pathway:** IgM or IgG required
 - **Alternative pathway:** nonspecifically triggered by substances on bacteria, yeast, viruses and protozoans - no antibody required.
- **Immune adherence:** a teamwork including complement, antibody, and phagocyte function together in the body's defense system.

Invertebrates have a rudimentary immune system

- Invertebrates depend on innate, nonspecific mechanisms of defense rather than acquired, antigen-specific mechanisms: phagocytosis, encapsulation, IL-1, immunoglobulin superfamily (hemolin), tissue grafting (immunological

memory), anti-microbial peptides, etc.

Immunity in Health and Disease

Immunity can be achieved naturally or artificially

- **Active immunity:** achieved antigens either naturally or artificially - **vaccination** or **immunization** of inactive or weakened form of the pathogen.
- **Passive immunity:** antibodies injection; temporary; the individual's own immune system has not been stimulated by the antigens;

The immune system's capacity to distinguish self from nonself limits blood transfusion and tissue transplantation

Blood groups and blood transfusion

- **ABO** blood group:
 - Type A person (only "A" antigen on the surface of their RBCs, and anti-B Ab, but not anti-A Ab in their serum), type B person, type AB person (both "A" and "B" antigen on the surface of their RBCs, and neither anti-A Ab or anti-B Ab in their serum), and type O person (No "A" or "B" antigen on the surface of their RBCs, and both anti-A Ab and anti-B Ab in their serum):
 - Blood group antigens are polysaccharides: IgM as generated Ab can not cross placenta, and no memory cells – T-independent.
- **Rh factor:** A pregnant woman antibodies react with the blood of her developing fetus. For example, Rh⁻ mother to Rh⁺ fetus:
 - Her response to the first exposure is mild and without medical care for the baby. The real danger occurs in the subsequent pregnancies: Her antibodies, IgGs, cross the placenta during the final week of gestation to destroy the RBCs of the fetus.

Tissue grafts and organ transplantation

- The **MHC** complicates tissue grafts and organ transplants: to match the MHC of the tissue donor and recipients as closely as possible.
- The rejection of the transplanted organ is attacked by **cytotoxic T cells**: cyclosporin A and FK506 can suppress helper T cell activation without reducing nonspecific defense or T-independent humoral responses.
- **Graft versus host reaction**: bone marrow transplant

Abnormal immune function can lead to disease

Allergies

- Hypersensitivities of the immune response to certain environmental antigens - **allergens** such as pollen:
 - typical allergy symptoms: sneezing, runny nose, tearing eyes, and smooth muscle contraction resulting breathing difficulty.
- **Mast cells** (non-circulating cells in connective tissue) in allergic reactions:
 - IgE bind on the surfaces of mast cells as allergen receptor.
 - Degranulation: releasing **histamine** and other inflammatory agents.
 - Anti-histamine block histamine receptor:
- **Anaphylactic shock**: acute allergic response causing by such as bee venom or penicillin.
 - When widespread mast cell degranulation triggers the abrupt dilation of peripheral blood vessels, blood pressure precipitously drops.
 - Death may occur within a few minutes: the patient with severe hypersensitivities should carry syringes containing epinephrine:

Autoimmune Diseases

- The immune system loses tolerance for self: The real mechanism is not well understood and may relate to viruses infection, drugs, or genetic mutations, which alter the surface components of some cells enough for them to be identified as foreign by the immune system. Also, it likely arises from some failure in immune regulation.
- **Systemic lupus erythematosus (lupus)**: autoantibodies against all sorts of self molecules.
- **Rheumatoid arthritis** leads to damage and painful inflammation of on cartilage and bone of joints.
- **Multiple sclerosis (MS)**: T cells destroy the myelin of neuron.

Immunodeficiency diseases

- **SCID** (Severe Combined Immuno-Deficiency): one kind of genetic disease - both humoral and cell-mediated immune systems fail to function.
 - Deficiency of the enzyme adenosine deaminase (ADA):
- **Hodgkin's disease**: Cancer cells damage the lymphatic system
- Physical and emotional stress can compromise immunity:
 - A network of nerve fibers penetrates into lymphoid tissue. Also, receptors for chemicals signals secrets by nerve cells have been discovered on the surfaces of lymphocytes.
 - Cortisone, one of glucocorticoids, secreted from adrenal gland during stress affect the number of WBCs.
 - Interferon levels are low during final exams:
 - Psycho-neuro-immunology & Immuno-neuro-endocrinology.

AIDS is an Immunodeficiency disease caused by a virus

- Acquired Immune Deficiency Syndrome (AIDS):

- People with AIDS are highly susceptible to **opportunistic diseases**.
- **Human Immunodeficiency Virus (HIV)** infects helper T cells and macrophages, which carry CD4 on their surfaces.
- HIV may remain latent for many years as a **provirus** integrated into the genome of an infected cell: The provirus is invisible to the host immune system.
- Peoples exposed to HIV have Abs against the virus: detection of this Abs is the common method to identify infected individuals--**HIV-positive**.
- HIV presents in breast milk, blood and semen: the route of HIV transmission involved nursing, intimate sexual contact, contaminated needles, and blood-to-blood contact, but rare by kissing or even casual contact.
- AIDS is incurable recently: Some drugs like DNA-synthesis inhibitors, reverse transcriptase inhibitors (AZT, ddI) and protease inhibitors may extend the lives of patients, but they do not completely eliminate the virus.