Immunopathology

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The immune system is a network of cells, tissues*, and organs that work together to defend the body against attacks by "foreign" invaders

microbes (germs)—tiny, infection-causing organisms such as bacteria, viruses, parasites, and fungi.

The immune system is amazingly complex. It can recognize and remember millions of different enemies, and it can produce secretions and cells to match up with and wipe out each one of them.

Self and Nonself

the key to a healthy immune system is its remarkable ability to distinguish between the body's own cells—self—and foreign cells—nonself. The body's immune defenses normally coexist peacefully with cells that carry distinctive "self" marker molecules. But when immune defenders encounter cells or organisms carrying markers that say "foreign," they quickly launch an attack. Anything that can trigger this immune response is called an antigen. An antigen can be a microbe such as a virus, or even a part of a microbe. Tissues or cells from another person (except an identical twin) also carry nonself markers and act as antigens. This explains why tissue transplants may be rejected.

In abnormal situations, the immune system can mistake self for nonself and attack against the body's own cells or tissues. The result is called an autoimmune disease. Some forms of arthritis and diabetes are autoimmune diseases. In other cases, the immune system responds to a seemingly harmless foreign substance such as ragweed pollen. The result is allergy, and this kind of antigen is called an allergen.

The Structure of the Immune System

The organs of the immune system are positioned throughout the body. They are called lymphoid organs because they are home to lymphocytes, small white blood cells that are the key players in the immune system.

Bone marrow, the soft tissue in the hollow center of bones, is the ultimate source of all blood cells, including white blood cells destined to become immune cells.

The thymus is an organ that lies behind the breastbone; lymphocytes known as T lymphocytes, or just "T cells," mature in the thymus. Lymphocytes can travel throughout the body using the blood vessels. The cells can also travel through a system of lymphatic vessels that closely parallels the body's veins and arteries. Cells and fluids are exchanged between blood and lymphatic vessels, enabling the lymphatic system to monitor the body for invading microbes. The lymphatic vessels carry lymph, a clear fluid that bathes the body's tissues.

lymph nodes, Small, bean-shaped are placed along the lymphatic vessels, with clusters in the neck, armpits, abdomen, and groin. Each lymph node contains specialized compartments where immune cells congregate, and where they can encounter antigens. Immune cells and foreign particles enter the lymph nodes via incoming lymphatic vessels or the lymph nodes' tiny blood vessels. All lymphocytes exit lymph nodes through outgoing lymphatic vessels. Once in the bloodstream, they are transported to tissues throughout the body. They patrol everywhere for foreign antigens, then gradually drift back into the lymphatic system, to begin the cycle all over again.

The spleen is a flattened organ at the upper left of the abdomen. Like the lymph nodes, the spleen contains specialized compartments where immune cells gather and work, and serves as a meeting ground where immune defenses confront antigens. Clumps of lymphoid tissue are found in many parts of the body, especially in the linings of the digestive tract and the airways and lungs—territories that serve as gateways to the body. These tissues include the tonsils, adenoids, and appendix.

Immune Cells and Their Products

The immune system stockpiles a huge arsenal of cells, not only lymphocytes but also cell-devouring phagocytes and their relatives. Some immune cells take on all comers, while others are trained on highly specific targets. To work effectively, most immune cells need the cooperation of their comrades. Sometimes immune cells communicate by direct physical contact, sometimes by releasing chemical messengers. The immune system stores just a few of each kind of the different cells needed to recognize millions of possible enemies. When an antigen appears, those few matching cells multiply into a full-scale army. After their job is done, they fade

All immune cells begin as immature stem cells in the bone marrow. They respond to different cytokines and other signals to grow into specific immune cell types, such as T cells, B cells, or phagocytes. Because stem cells have not yet committed to a particular future, they are an interesting possibility for treating some immune system disorders. Researchers currently are investigating if a person's own stem cells can be used to regenerate damaged immune responses in autoimmune diseases and immune deficiency diseases.

B Lymphocytes

B cells work chiefly by secreting substances called **antibodies** into the body's fluids. Antibodies ambush antigens circulating the bloodstream. They are powerless, however, to penetrate cells. The job of attacking target cells—either cells that have

been infected by viruses or cells that have been distorted by cancer—is left to T cells or other immune cells.

An antigen matches an antibody much as a key matches a lock. Some match exactly; others fit more like a skeleton key. But whenever antigen and antibody interlock, the antibody marks the antigen for destruction. Antibodies belong to a family of large molecules known as immunoglobulins. Different types play different roles in the immune defense strategy.

- Immunoglobulin G, or IgG, works efficiently to coat microbes, speeding their uptake by other cells in the immune system. IgM is very effective at killing bacteria. • IgA concentrates in body fluids—tears, saliva, the secretions of the respiratory tract and the digestive tract—guarding the entrances to the body.
- IgE, whose natural job probably is to protect against parasitic infections, is the villain responsible for the symptoms of allergy.
- IgD remains attached to B cells and plays a key role in initiating early B-cell response.

T Cells Unlike B cells, T cells do not recognize free-floating antigens. Rather, their surfaces contain specialized antibody-like receptors that see fragments of antigens on the surfaces of infected or cancerous cells. T cells contribute to immune defenses in two major ways: some direct and regulate immune responses; others directly attack infected or cancerous cells.

Helper T cells, or Th cells, coordinate immune responses by communicating with other cells. Some stimulate nearby B cells to produce antibody, others call in microbegobbling cells called phagocytes, still others activate other T cells.

Killer T cells—also called cytotoxic T lymphocytes or CTLs—perform a different function. These cells directly attack other cells carrying certain foreign or abnormal molecules on their surfaces. CTLs are especially useful for attacking viruses because viruses often hide from other parts of the immune system while they grow inside infected cells. CTLs recognize small fragments of these viruses peeking out from the cell membrane and launch an attack to kill the cell.

T cells only recognize an antigen if it is carried on the surface of a cell by one of the body's own MHC, or major histocompatibility complex, molecules. MHC molecules are proteins recognized by T cells when distinguishing between self and nonself. A self MHC molecule provides a recognizable scaffolding to present a foreign antigen to the T cell.

Although MHC molecules are required for T-cell responses against foreign invaders, they also pose a difficulty during organ transplantations. Virtually every cell in the body is covered with MHC proteins, but each person has a different set of these

proteins on his or her cells. If a T cell recognizes a nonself MHC molecule on another cell, it will destroy the cell. Therefore, doctors must match organ recipients with donors who have the closest MHC makeup. Otherwise the recipient's T cells will likely attack the transplanted organ, leading to graft rejection.

Natural killer (NK) cells are another kind of lethal white cell, or lymphocyte. Like killer T cells, NK cells are armed with granules filled with potent chemicals. But while killer T cells look for antigen fragments bound to self-MHC molecules, NK cells recognize cells lacking self-MHC molecules. Thus NK cells have the potential to attack many types of foreign cells. Both kinds of killer cells slay on contact. The deadly assassins bind to their targets, aim their weapons, and then deliver a lethal burst of chemicals.

Phagocytes and Their Relatives

Phagocytes are large white cells that can swallow and digest microbes and other foreign particles. Monocytes are phagocytes that circulate in the blood. When monocytes migrate into tissues, they develop into macrophages. Specialized types of macrophages can be found in many organs, including lungs, kidneys, brain, and liver. 14 Macrophages play many roles. As scavengers, they rid the body of worn-out cells and other debris. They display bits of foreign antigen in a way that draws the attention of matching lymphocytes. And they churn out an amazing variety of powerful chemical signals, known as monokines, which are vital to the immune responses.

Granulocytes are another kind of immune cell. They contain granules filled with potent chemicals, which allow the granulocytes to destroy microorganisms. Some of these chemicals, such as histamine, also contribute to inflammation and allergy. One type of granulocyte, the neutrophil, is also a phagocyte; it uses its prepackaged chemicals to break down the microbes it ingests. Eosinophils and basophils are granulocytes that "degranulate," spraying their chemicals onto harmful cells or microbes nearby.

The mast cell is a twin of the basophil, except that it is not a blood cell. Rather, it is found in the lungs, skin, tongue, and linings of the nose and intestinal tract, where it is responsible for the symptoms of allergy.

Cytokines

Components of the immune system communicate with one another by exchanging chemical messengers called cytokines. These proteins are secreted by cells and act on other cells to coordinate an appropriate immune response. Cytokines include a diverse assortment of interleukins, interferons, and growth factors. Some cytokines are chemical switches that turn certain immune cell types on and off.

One cytokine, interleukin 2 (IL-2), triggers the immune system to produce T cells. IL2's immunity-boosting properties have traditionally made it a promising treatment for several illnesses. Clinical studies are ongoing to test its benefits in other diseases such as cancer, hepatitis C, and HIV infection and AIDS. Other cytokines also are being studied for their potential clinical benefit. Other cytokines chemically attract specific cell types. These so-called chemokines are released by cells at a site of injury or infection and call other immune cells to the region to help repair the damage or fight off the invader. Chemokines often play a key role in inflammation and are a promising target for new drugs to help regulate immune responses.

complement

The complement system is made up of about 25 proteins that work together to "complement" the action of antibodies in destroying bacteria. Complement also helps to rid the body of antibody-coated antigens (antigen-antibody complexes). Complement proteins, which cause blood vessels to become dilated and then leaky, contribute to the redness, warmth, swelling, pain, and loss of function that characterize an inflammatory response. Complement proteins circulate in the blood in an inactive form. When the first protein in the complement series is activated— typically by antibody that has locked onto an antigen—it sets in motion a domino effect. Each component takes its turn in a precise chain of steps known as the complement cascade.

Immunity: Natural and Acquired

Long ago, physicians realized that people who had recovered from the plague would never get it again—they had acquired immunity. This is because some of the activated T and B cells become memory cells. The next time an individual meets up with the same antigen, the immune system is set to demolish it. Immunity can be strong or weak, short lived or long-lasting, depending on the type of antigen, the amount of antigen, and the route by which it enters the body.

Immunity can also be influenced by inherited genes. When faced with the same antigen, some individuals will respond forcefully, others feebly, and some not at all.

An immune response can be sparked not only by infection but also by immunization with vaccines. Vaccines contain microorganisms—or parts of microorganisms—that have been treated so they can provoke an immune response but not full-blown disease. Immunity can also be transferred from one individual to another by injections of serum rich in antibodies against a particular microbe (antiserum). For example, immune serum is sometimes given to protect travelers to countries where hepatitis A is widespread. Such passive immunity typically lasts only a few weeks or months.

MECHANISMS OF HYPERSENSITIVITY REACTIONS

- ***Hypersensitivity reactions*** are immune responses to exogenous or endogenous antigens resulting in tissue injury that caused by humoral or cell-mediated immune mechanisms.

Most hypersensitivity diseases show a genetic predisposition. The MHC genes are particularly associated with hypersensitivity diseases, but many non-MHC genes also play a role.

Types of hypersensitivity disorders

- **Immediate (type I) hypersensitivity**
- **Antibody-mediated (type II) hypersensitivity**
- **Immune complex-mediated (type III) hypersensitivity**
- **Cell-mediated (type IV) hypersensitivity**

Immediate (Type I) Hypersensitivity

This is a rapidly developing immune reaction occurring within minutes after the combination of an antigen with IgE bound to mast cells or basophils in individuals previously sensitized to the antigen (allergen).

Immediate (type I) Hypersensitivity

A. Systemic Reaction

Injection of a druge.g. penicillin(Anaphylactic shock Within minutes

B. Local Reactions

-10 %of population

-Urticaria

-Allergic rhinitis

-Allergic conjunctivitis

-Allergic gastroenteritis food allergy (Hay fever- Bronchial asthma

Many local type I hypersensitivity reactions have two well-defined phases: The initial response is characterized by vasodilation ،increased vascular permeability and depending on the location ،smooth muscle spasm or increased glandular secretions .

These changes usually become evident within 5 to 30 minutes after exposure to an allergen and tend to subside in 60 minutes .

A late-phase reaction sets in 2 to 24 hours later without additional exposure to antigen in many instances (e.g., allergic rhinitis and bronchial asthma), and may last for several days. It is characterized by infiltration of tissues with eosinophils, neutrophils, basophils, monocytes, and CD4+ T cells as well as tissue destruction, typically in the form of mucosal epithelial cell damage.

The susceptibility to immediate hypersensitivity reactions is genetically determined .

The term atopy refers to a predisposition to develop localized immediate hypersensitivity reactions to a variety of inhaled and

ingested allergens .Atopic individuals tend to have higher serum IgE levels compared with the general population .A positive family history of allergy is found in 50% of atopic individuals.

Antibody-Mediated (Type II) Hypersensitivity

Is mediated by antibodies directed toward antigens present on cell surfaces or extracellular matrix .The antigenic determinants may be intrinsic to the cell membrane or matrix, or they may be an exogenous antigen e.g. a drug metabolite that is adsorbed on a cell surface or matrix . In either case, the hypersensitivity reaction results from the binding of antibodies to normal or altered cell-surface antigens. Three different antibody-dependent mechanisms which usually involve the complement system and phagocytes :

1- Opsonization &Complement- & Fc Receptor-Mediated Phagocytosis
2- Antibody-dependent cellular cytotoxicity
3- Antibody-Mediated Cellular Dysfunction

1-Opsonization and Complement- and Fc Receptor-Mediated Phagocytosis

Antibodies (of the IgM or IgG class) deposited on the surfaces of targeted cells, may activate the complement system generating byproducts including C3b and C4b that are opsonins which when deposited on the surfaces of the cells and recognized by phagocytes that express receptors for these proteins result in the phagocytosis of the opsonized cells and their destruction .The membrane attack complex, which disrupts

membrane integrity by "drilling holes" through the lipid bilayer, thereby causing osmotic lysis of the cells.

2- Antibody-dependent cellular cytotoxicity (ADCC)

Cells that are coated with low conc. of IgG antibody are killed by a variety of effector cells (including monocytes, neutrophils, eosinophils, and NK cells) which bind to the target by their receptors for the Fc fragment of IgG, and cell lysis proceeds without phagocytosis .

In eosinophil-mediated cytotoxicity against parasites, IgE antibodies are used.

3-Antibody-Mediated Cellular Dysfunction

In some cases, antibodies directed against cell-surface receptors impair or dysregulate function without causing cell injury or inflammation e.g. In myasthenia gravis where antibodies reactive with acetylcholine receptors in the motor end-plates of skeletal muscles lead to impair neuro- muscular transmission that result muscle weakness . In Grave's disease where antibodies against the TSH- receptors on thyroid epithelial cells stimulate the cells causing hyperthyroidism.

Clinical examples antibody-mediated cell destruction and phagocytosis

(1) transfusion reactions, in which cells from an incompatible donor react with and are opsonized by preformed antibody in the host.
(2) Erythroblastosis fetalis, in which antibodies (of the IgG class) from a sensitized Rh negative mother cross the placenta and cause destruction of Rh positive fetal red cells .

(3) Autoimmune hemolytic anemia, agranulocytosis, and thrombocytopenia, in which individuals produce antibodies to their own blood cells, which arethen destroyed .

(4) Certain drug reactions, in which antibodies that react with the drug, which may be attached to the surface of erythrocytes or other cells.

Immune Complex-Mediated (Type III) Hypersensitivity

Antigen-antibody complexes produce tissue damage mainly by eliciting inflammation at the sites of deposition .

The mere formation of antigen-antibody complexes in the circulation does not imply the presence of disease ؛Immune complexes are formed in many immune responses and represent a normal mechanism of antigen removal.

Two general types of antigens cause immune complex-mediated injury :

(1) The antigen may be exogenous, such as a foreign protein, a bacterium, or a virus; or

(2) Endogenous (self) antigens, which can be circulating antigens present in the blood or, antigenic components of one's own cells and tissues .

Immune complex-mediated diseases can be:

(1)- generalized, if immune complexes are formed in the circulation and are deposited in many organs, or

(2)- localized to particular organs, such as the kidney (glomerulonephritis), joints (arthritis), or the small blood vessels of the skin (vasculitis) if the complexes are formed and deposited locally.

Three phases are recognized in pathogenesis of systemic immune complex disease :

(1) formation of Ag-Ab complexes in the circulation ؛
(2) deposition of the immune complexes in various tissues, thus initiating
(3) an inflammatory reaction at the sites of immune complex deposition

The factors that determine whether immune complex formation will lead to tissue deposition and disease are not fully understood, but two possible influences are :

1 -Size of the immune complexes: Large complexes formed in great antibody excess are rapidly removed from the circulation by the mononuclear phagocyte system and are therefore relatively harmless. The most pathogenic complexes are of small or intermediate size (formed in slight antigen excess), which bind less avidly to phagocytic cells and therefore circulate longer .

2- The functional status of the mononuclear phagocyte system: Because the mononuclear phagocyte system normally filters out the circulating immune complexes, its overload or intrinsic dysfunction increases the probability of persistence of immune complexes in circulation and tissue deposition. Favored sites of

immune complex deposition are the renal glomeruli, joints, skin, heart, serosal surfaces, and small blood vessels.

For complexes to leave the microcirculation and deposit in the vessel wall, an increase in vascular permeability must occur. This is believed to occur when immune complexes bind to inflammatory cells through their Fc or C3b receptors and trigger release of vasoactive mediators as well as permeability-enhancing cytokines .

The complexes deposited in the tissues, initiate an acute inflammatory reaction (third phase). During this phase (approximately 10 days after antigen administration), fever, urticaria, arthralgias, lymph node enlargement, and proteinuria appear.

Two mechanisms are believed to cause inflammation at the sites of deposition

1-activation of the complement cascade, and

2-activation of neutrophils and macrophages through their Fc receptors release or generation of a variety of pro-inflammatory substances and subsequent tissue damage

Cell-Mediated (Type IV) Hypersensitivity

The cell-mediated type of hypersensitivity is initiated by antigen-activated (sensitized) T lymphocytes. It includes:

The delayed type hypersensitivity reactions mediated by CD4+ T cells, and direct cell cytotoxicity mediated by CD8+ T cells .

It is the principal pattern of immunologic response to intracellular microbiologic agents, such as T.B. & also to many viruses, fungi, protozoa, and parasites .

Contact skin sensitivity to chemical agents ، graft rejection, and many autoimmune diseases like type I diabetes mellitus and multiple sclerosis are now known to be caused by T cell-mediated reactions.

Delayed Type Hypersensitivity

This is the principal pattern of response to T.B., fungi, protozoa, parasites, contact dermatitis and also contributes to graft rejection.

Disorders of the Immune System

Allergic Diseases

The most common types of allergic diseases occur when the immune system responds to a false alarm. In an allergic person, a normally harmless material such as grass pollen or house dust is mistaken for a threat and attacked. Allergies such as pollen allergy are related to the antibody known as IgE. Like other antibodies, each IgE antibody is specific; one acts against oak pollen, another against ragweed.

Autoimmune Diseases

Sometimes the immune system's recognition apparatus breaks down, and the body begins to manufacture T cells and antibodies directed against its own cells and organs. Misguided T cells and autoantibodies, as they are known, contribute to many diseases. For instance, T cells that attack pancreas cells contribute to diabetes, while an autoantibody known as rheumatoid factor is common in people with rheumatoid arthritis. People with systemic lupus erythematosus (SLE) have antibodies to many types of their own cells and cell components. No one knows exactly what causes an autoimmune disease, but multiple factors are likely to be involved. These include elements in the environment, such as viruses, certain drugs, and sunlight, all of which may damage or alter normal body cells. Hormones are suspected of playing a role, since most autoimmune diseases are far more common in women than in men.

Heredity, too, seems to be important. Many people with autoimmune diseases have characteristic types of self marker molecules.

Immune Complex Diseases

Immune complexes are clusters of interlocking antigens and antibodies. Normally, immune complexes are rapidly removed from the bloodstream. Sometimes, however, they continue to circulate, and eventually become trapped in the tissues of the kidneys, the lungs, skin, joints, or blood vessels. There they set off reactions with complement that lead to inflammation and tissue damage. Immune complexes work their mischief in many diseases. These include malaria and viral hepatitis, as well as many autoimmune diseases.

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Acute serum sickness: is the prototype of a systemic immune complex disease; Previously was a frequent outcome of administrating large amounts of foreign immune serum for passive immunization e.g. antidiphtheria toxin immune serum from These patients developed arthritis, skin rash, and fever, and the symptoms appeared more rapidly with repeated injection of the serum .

Immunodeficiency Disorders

When the immune system is missing one or more of its components, the result is an immunodeficiency disorder. Immunodeficiency disorders can be inherited, acquired through infection, or produced unintentionally by drugs such as those used to treat people with cancer or those who have received transplants. Temporary immune deficiencies can develop in the wake of common virus infections, including influenza,

infectious mononucleosis, and measles. Immune responses can also be depressed by blood transfusions, surgery, malnutrition, smoking, and stress.

Some children are born with poorly functioning immune systems. Some have flaws in the B cell system and cannot produce antibodies. Others, whose thymus is either missing or small and abnormal, lack T cells. Very rarely, infants are born lacking all of the major immune defenses. This condition is known as severe combined immunodeficiency disease or SCID.

AIDS is an immunodeficiency disorder caused by a virus (HIV) that infects immune cells. HIV can destroy or disable vital T cells, paving the way for a variety of immunologic shortcomings. HIV also can hide out for long periods in immune cells. As the immune defenses falter, a person with AIDS falls prey to unusual, often life-threatening infections and rare cancers. A contagious disease, AIDS is spread by intimate sexual contact, transfer of the virus from mother to infant during pregnancy, or direct blood contamination. There is no cure for AIDS, but newly developed antiviral drugs can slow the advance of the disease, at least for a time. Researchers also are testing HIV vaccines in clinical studies.