Components and Diseases of the Human Immune System

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The physiological structure and function of the human immune system are key issues in the academic education of physicians and other medical professionals. In order to recognize pathogeneses on the micro- and macro-biological level at an early stage, and to be able to treat them adequately, comprehensive knowledge of physiological and pathophysiological processes is required. Due to demographic changes, a continuous increase in psychosomatic diseases by immunosuppression can be observed. Therefore, besides an effective treatment with medication, physicians should also offer their patients possibilities for an autonomous strengthening of the immune system, for example by changing their nutrition and lifestyle.

Definition

The human immune system is the biological defense system of the body and consists of specialized cells and organs. Its functions are to combat and eliminate pathogens that infiltrate the body. These pathogens could be bacteria, viruses, fungi, or parasites. Physiologically, the human immune system comprises the nonspecific and specific immune systems.

Nonspecific immune system

The nonspecific immune system, also known as the innate immune response, is composed of the cellular and humoral nonspecific defenses. Both systems are complementary in their functions.

The cellular nonspecific immune response includes macrophages and neutrophils, which destroy harmful microorganisms by phagocytosis. This immune response also involves other cell types.

As part of the humoral nonspecific immune response, enzymes, i.e., non-cellular soluble components of the immune response or endogenous messenger substances, recruit immune cells to combat pathogens.

Specific immune system

The primary components of the specific immune response are the B lymphocytes and their antibodies (humoral immune response) as well as the T lymphocytes (cellular immune response). The specific immune response also includes antigens and antibodies as well as plasma cells, which result in a faster response if the same pathogen reinfects the system.

Components of the Immune System

The micro-level, which includes the cellular components, is distinguished from the macro-level, which represents the organs of the immune system.

Components of the cellular nonspecific immune response

Monocytes

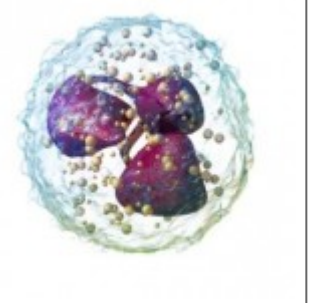
Monocytes are phagocytes with the additional ability to expose foreign substances to the specific immune system.

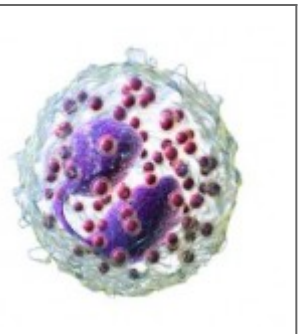
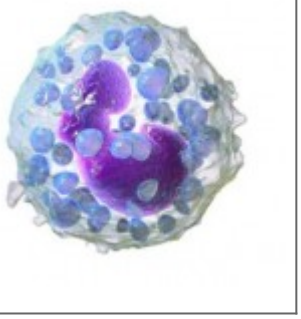
Macrophages

Macrophages are phagocytes that develop from monocytes and specialize depending on their location. Thus, a macrophage that is located in the connective tissue is called a histiocyte.

Granulocytes

Granulocytes are leukocytes and are divided into 3 types:

Neutrophil granulocytes	• Phagocytes that infiltrate tissue when attracted to the pathogens via the influence of chemotaxins.	

Eosinophil granulocytes	• Granulated phagocytes that become activated by histamine and are, therefore, particularly active in allergic reactions.	
Basophil granulocytes	• In addition to their phagocytic function, they have the ability to release heparin, histamine, and proteases from their granules.	

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Components of the humoral nonspecific immune response

Lysozyme

The lysozyme is defined as a type of enzyme that destroys the cell wall of bacteria and can be found in saliva, tear fluid, etc.

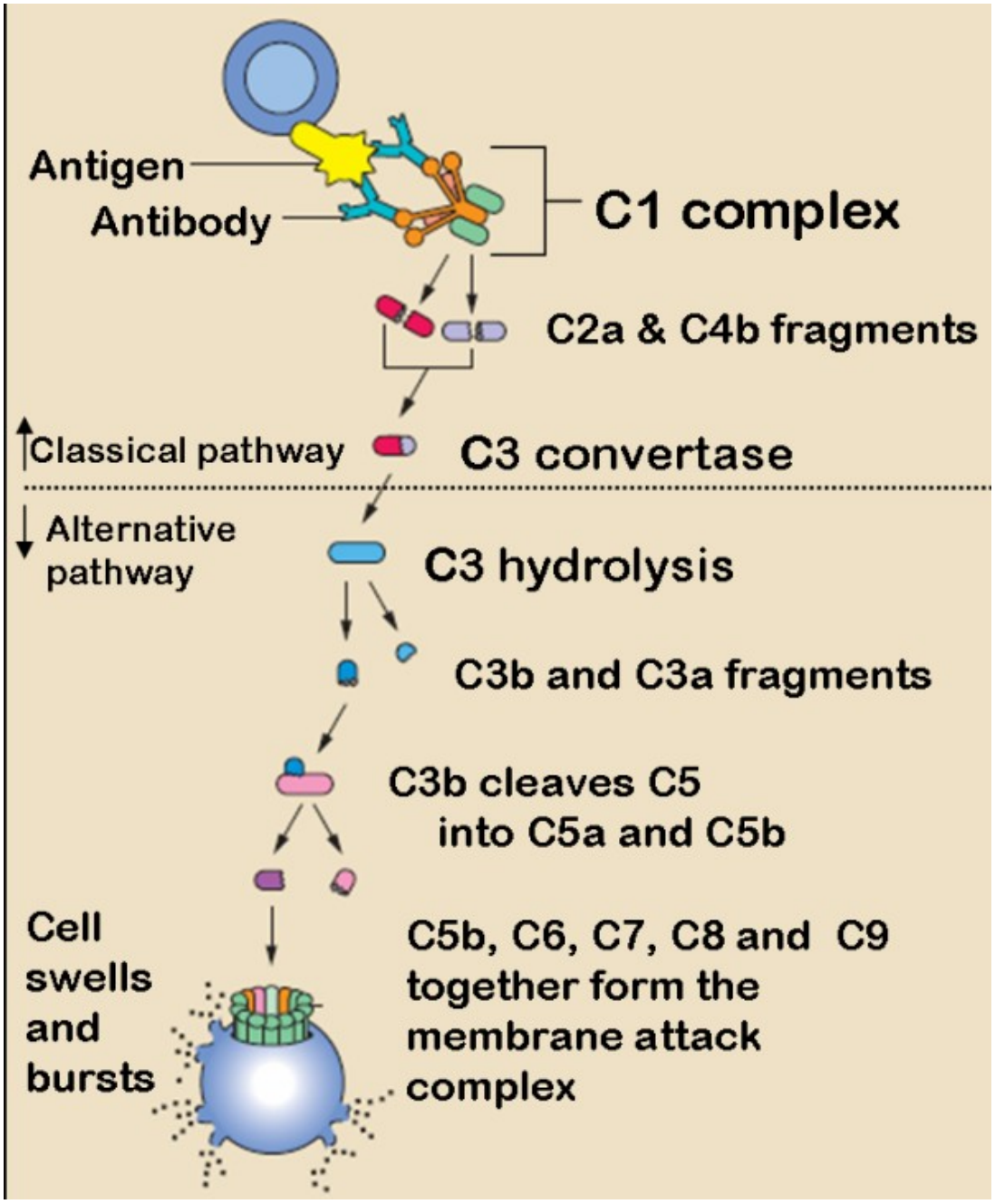
Cytokines

Cytokines are messenger substances that aid communication between leukocytes. Thus, they provide a coordinated immune response to pathogens. There are 3 different types of cytokines as follows:

Interferons	• Serve primarily as viral and tumor defense • Belong to the glycoproteins and are divided into alpha, beta, gamma, and tau interferons
Interleukin-6	• Synthesize proteins in the liver during an acute immune response
Tumor necrosis factor-alpha	• Active in local and systemic inflammations

The complement system

The complement system consists of various plasma proteins that attach to pathogens in order to attract phagocytes and leukocytes. Thus, they are directly involved in the elimination of cellular antigens.



Components of the specific immune response

Antigen

The antigen is the immune response-inducing protein of a pathogen. In the immune response, they are either bound to antibodies or to the receptors of lymphocytes and are eliminated.

Antibodies

Antibodies are immunoglobulins that are formed by plasma cells, which, in turn, are derived from B lymphocytes. There are 5 types of antibodies:

	IgM pentamer	IgG monomer	IgA dimer	IgE monomer	IgD monomer

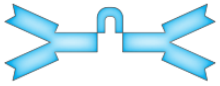
					
Heavy chains	μ	γ	α	ε	δ
Number of antigen-binding sites	10	2	4	2	2
Molecular weight (Daltons)	900,000	150,000	385,000	200,000	180,000
Percentage of total antibody in serum	6%	80%	13%	0.002%	1%
FC binds to		Phagocytes		Mast cells and Basophils	
Function	The main antibody for primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor.	Main blood antibody for secondary responses, neutralizes toxins, opsonization	Secreted into mucus, tears, saliva, colostrum	Antibody for allergy and antiparasitic activity	B cell receptor

Table based on Phil Schatz. Image: Monomere and Polymere. By: Martin Brändli (brandlee86). License: CC BY-SA 2.5

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B lymphocytes

B lymphocytes are cells of the humoral immune defense which, after antigen contact with the B lymphocyte receptor, turn into plasma cells and B memory cells through cell division.

The plasma cells produce antibodies (immunoglobulins) in the Golgi apparatus and endoplasmic reticulum of the cell and are, therefore, defined as the ‘actual antibody producers’.

After the initial infection, the B memory cells remain in the body and lead to a faster immune response in case of reinfection with the same pathogen.

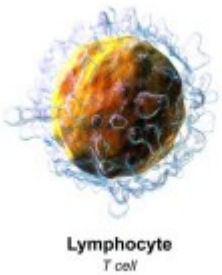


Image: T cell. By: Blausen gallery 2014. License: CC BY 3.0

T lymphocytes

T lymphocytes originate from stem cells in the bone marrow and migrate to the thymus where they mature and specialize.

Upon activation of antigen-presenting cells, T helper cells bind to B lymphocytes in order to secrete cytokines.

The functions of cellular immunity are carried out by cytotoxic cells or T killer cells. With their receptors, they bind to exogenous or infected cells and destroy them using perforins (destruction of the pathogen cell membrane) and granzymes that penetrate the foreign cell and cause apoptosis (cell death).

Immunological memory, on the other hand, is achieved by the T memory cells, whose immunological function is comparable to that of the B memory cells.

Antigen-presenting cells
Antigen-presenting cells are specialized interdigitating dendritic cells that internalize intruding antigens and migrate to T cell areas and lymph nodes in order to present the antigens to the specific immune response.

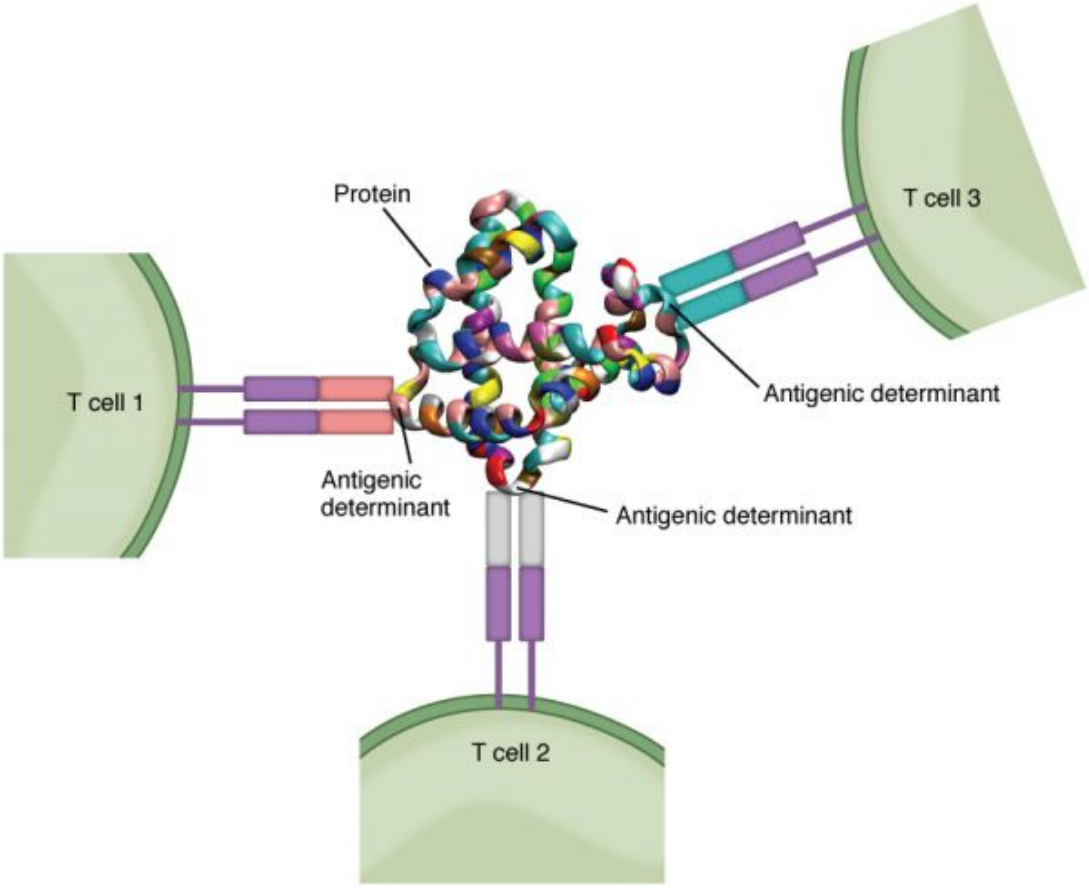


Image: Antigenic Determinants. By: Phil Schatz. License: CC BY 4.0

Components of the organic immune defense

The lymphatic system consists of organs that produce, specialize, and locate immune-active cells. This system is divided into the primary and secondary lymphatic systems.

The primary lymphatic system includes the bone marrow and thymus.

The secondary lymphatic system consists of the lymphoepithelial organs (palatine tonsils,

pharyngeal tonsil, tubal tonsils, and lingual tonsils), mucosa-associated lymphoid tissue (MALT), and lymphoreticular organs, which include the lymph nodes and spleen.

Physiology of the Immune System

The immune response becomes effective when the body is confronted by pathogens. It is important to know that the immune response only starts the moment a pathogen overcomes the mechanical protective barriers of the body. The types of immune responses can be classified based on various parameters.

Classification according to time of development

In this classification, the nonspecific innate immune response is distinguished from the adaptive specific response.

Nonspecific innate immune response

In the nonspecific immune response, the pathogen is first engulfed and destroyed by phagocytes. This is the so-called receptor-mediated phagocytosis, which is performed by macrophages and granulocytes. The emerging fragments of the pathogen are then presented to the cells of the specific immune defense (B and T lymphocytes)—a process that is called opsonization.

Adaptive specific immune response

The adaptive specific immune response is directed against a specific antigen that is already known to the body. Two systems of adaptive immunity protect all vertebrates, namely, cellular and humoral immunity. In cellular defense, the T lymphocytes are active, while in humoral defense, the antibodies of B lymphocytes are active. For viral infections, cytotoxic T cells (killer T cells) are activated by the presented antigen and destroy the foreign cell using perforins and granzymes. The effects of both classes of immune responses may be harmful or beneficial and are mediated by cells of the highly distributed lymphoid system.

Innate immune response	Adaptive immune response
Broad specificity for pathogen-associated molecular patterns (PAMPs)	High specificity for antigen
Same intensity every time	Stronger and faster on reinfection (primary vs. secondary immune response—immunological memory)
Rapid response (minutes to hours): cells already in body tissue or recruited directly from blood circulation	Initially, rather slow response (days): cells need to proliferate in secondary lymphoid tissues.

The adaptive specific immune response is more complex than the innate response. **It is characterized by the following:**

1. Antigen specificity: It permits the immune response to distinguish subtle differences between antigens. Antibodies can differentiate between 2 molecules that differ by a single amino acid (binding block of proteins).
2. Diversity: It is capable of generating notable diversity in its recognition molecules, allowing it to specifically recognize billions of uniquely different structures on foreign antigens.
3. Immunologic memory: Once the immune system has recognized and responded to an antigen, a second encounter with the same antigen induces a heightened state of immune reactivity.

4. Self/none self-recognition: The immune system normally responds only to foreign antigens indicating that it is capable of self/none self-recognition.

Within the specific immune response, it is important to make a distinction with regard to the major histocompatibility complex (MHC), as there are responses of Class I and Class II MHC molecules. MHC molecules are integral plasma membrane proteins that are important in antigen presentation during the immune response.

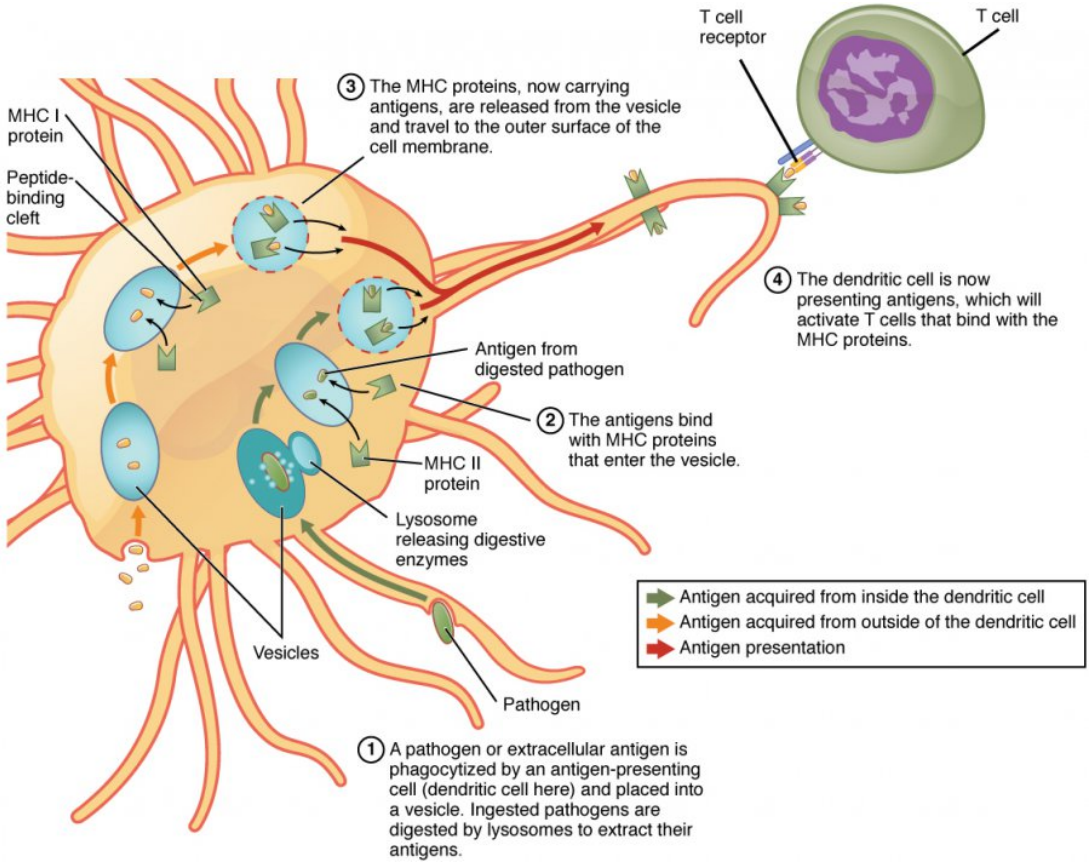
1. **Class I MHC-mediated immune reaction:**
   During a viral infection, viruses infiltrate the cells of the body and synthesize protein complexes that are transferred to a class I MHC molecule. Cytotoxic T lymphocytes recognize the change in the MHC complex and destroy the cell.
2. **Class II MHC-mediated immune response:**
   Class II MHC proteins are located on the surface of antigen-presenting cells and can bind foreign antigens prior to internalizing them into the endosome. Thereby, fragments of the antigens enter the class II MHC complex, which is then recognized by helper T cells. After that, the helper T cells initiate the specific immune response to the recognized antigen.

Adaptive immunity is often subdivided into 2 major types depending on how the immunity was introduced.

- Naturally acquired immunity occurs through non-deliberate contact with a disease-causing agent.
- Artificially acquired immunity develops only through deliberate actions such as vaccination.

Both naturally and artificially acquired immunity can be further subdivided depending on whether immunity is induced in the host or passively transferred from an immune host. Thus, we have the following:

Passive immunity is acquired through the transfer of antibodies or activated T cells from an immune host and is short-lived, usually lasting only a few months, whereas **active immunity** is induced in the host by an antigen, and lasts much longer, sometimes throughout life. The figure below summarizes these types of immunity.



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Classification according to involved components

In this classification, there is an important distinction between the cellular and humoral immune responses.

Cellular immune response
The cellular immune response refers to the immune response of T cells to an antigen that is destroyed by perforins and granzymes.

Humoral immune response
As part of the humoral immune response, B lymphocytes produce antibodies against known pathogens and release them into the serum. Here, it is important to differentiate the processes outside the lymph follicle from those within the lymph follicle. Lymph follicles are nodular accumulations of B lymphocytes. Therefore, they are important structures in the humoral immune response.

1. **Processes outside the lymph follicle**
   Helper T cells located outside the lymph follicle respond to the antigen presented by antigen-presenting cells by proliferating. They then bind to B lymphocytes and stimulate them to secrete cytokines.
2. **Processes within the lymph follicle**
   The proliferation of B lymphocytes takes place in the germinal center of the lymph follicle. The resident dendritic cells present antigens that have been previously internalized in the lymph and blood. Provided that such an antigen matches one of the receptors of the produced B lymphocytes, they proliferate to centroblasts. If they have a high affinity for the antigen, they are transformed into plasma cells or B memory cells. If because of mutations, a centroblast has little or no affinity for

the antigens, it is either destroyed by apoptosis or phagocytosed by macrophages.

Classification by contact history

Contact history describes the frequency with which the body has come into contact with an antigen. Initial contact with the antigen results in a primary immune response, while renewed contact with the same antigen results in a secondary immune response.

Primary immune response
The primary immune response represents the immunological response to a new antigen at initial contact. Here, immunoglobulins (IgM by B lymphocytes) are released as part of the humoral defense. At first, this immunoglobulin only has a weak affinity to the new antigen; therefore, additional high-affinity IgG and IgA are released into the serum to accelerate the initially slow immune response. To ensure a faster immune response to any future infection by the same pathogen, antigen-specific B memory cells remain in the body after the antigen is destroyed by phagocytes. This renewed immune response is referred to as a secondary immune response.

Secondary immune response
In the secondary immune response, the pathogen or antigen is already known to the immune system and memorized in the B memory cells. Therefore, compared to the primary immune response, significantly less IgM is released into the body by B lymphocytes, and the body can more readily use the high-affinity immunoglobulins (IgG and IgA).

Diseases of the Immune System

There is a specific difference between 2 forms of immunopathology: autoimmune diseases and allergies.

Autoimmune diseases

In autoimmune disease, antibodies attack endogenous tissue. Here, the physiologic immune tolerance a person has acquired during his/her lifetime is lost. Well-known examples are juvenile diabetes mellitus, ulcerative colitis, or autoimmune thyroiditis (Hashimoto’s disease). One possible treatment is immunosuppressant therapy; however, this is not directed at the cause and only provides symptom relief by alleviating the autoimmune reaction.

Disease	Autoantigen	Symptoms
Celiac disease	Transglutaminases	Damage of the small intestine
Diabetes mellitus type I	Beta cells of the pancreas (islets of Langerhans)	Low insulin production; inability to absorb glucose from the blood into the body cells
Hashimoto’s thyroiditis	Thyroid-stimulating hormone receptor (antibody blocks receptor)	Hypothyroidism
Graves’ disease	Thyroid-stimulating hormone receptor (antibody mimics hormones and stimulates receptor)	Hyperthyroidism
Lupus erythematosus	Nuclear DNA and proteins	Damage of various physical functions

Myasthenia gravis	Acetylcholine receptors of the neuromuscular system	Muscle weakness
Rheumatoid arthritis	Antigens in the joint capsule	Chronic inflammation of the joints

Allergies

Allergies are hypersensitivity reactions of the immune system to one or more certain antigens. Any substance that can elicit an allergic response is referred to as an allergen. However, an allergen can only be effective in causing an allergic reaction if the recipient has been previously sensitized i.e. antibodies of the IgE class directed against the allergen must be present in the tissues. A predisposition to allergies is called atopy. Typical allergy-related diseases include asthma, hay fever, or eczema. There are 4 basic types of allergic reactions, which are caused by different immunoglobulins.

Allergies are treated via desensitization therapy with allergen extracts either subcutaneously (SCIT) or sublingually (SLIT). This therapy involves deliberate immunization with small but increasing amounts of a particular purified allergen over months or years. The effectiveness of this procedure is thought to result from the induction of high levels of IgG antibodies, which can prevent allergic reactions by competing for the allergen and preventing it from reaching mast cell-bound IgE.

Avoidance of allergens is the single most important and effective method of managing allergic states. This may include eliminating known allergens from one’s diet (nuts, milk, eggs, etc).

Drugs can be useful for preventing and treating allergic reactions. Antihistamines inhibit the binding of histamine to its receptors (but will not affect the target tissue response once histamine is bound). Corticosteroids are anti-inflammatory (useful for the late-phase response), and can also inhibit histamine synthesis. Cromolyn sodium is known to stabilize mast cells.

Isoproterenol, salbutamol, and epinephrine can be used to counteract the effects of several of the mediators released by mast cells, and unlike the drugs mentioned above, they can be effective in controlling an ongoing allergic reaction. Prompt treatment of a systemic anaphylactic reaction (to food, drug, or insect bite, for example) can be lifesaving. For very severe allergies, immunosuppressants can be administered.

Diagnostic tests for immediate hypersensitivity include:

- Skin (prick and intradermal) tests
- Measurement of total IgE and specific IgE antibodies against the suspected allergens

Total IgE and specific IgE antibodies are measured by a modification of the enzyme immunoassay (ELISA).

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Notes