IMMUNOLOGY

HYPERSENSITIVITY

Hypersensitivity Reactions

Content

Learning objective

Overview

Type 1 Hypersensitivity

Type II Hypersensitivity

- Cytotoxic type
- Non-Cytotoxic type (Also Know as Type V)

Type III Hypersensitivity

Type IV Hypersensitivity

Pathology of autoimmunity

Chapter Summary

Hypersensitivity Reactions

Learning Objectives

❑❑ Differentiate type I (immediate), type II (antibody-mediated), type III (immune complex), and type IV (T-cell-mediated) hypersensitivity

❑❑ Answer questions about the pathogenesis of autoimmunity

Hypersensitivity Reactions

Overview

Hypersensitivity diseases are conditions in which tissue damage is caused by immune responses. They may result from uncontrolled or excessive responses against **foreign** antigens or from a **failure of self-tolerance**, in which case they are called **autoimmune diseases**.

The 2 principal factors which determine the clinical and pathologic consequences of such conditions are the **type of immune response** elicited and the **nature and location of the inciting antigen**. What the hypersensitivity reactions have in common:

- The first exposure to the antigen "sensitizes" lymphocytes.
- Subsequent exposures elicit a damaging reaction.
- The response is specific to a particular antigen or a cross-reacting substance.

Hypersensitivity Reactions

Hypersensitivity diseases are classified on the basis of the effector mechanism responsible for tissue injury, and 4 types are commonly recognized.

- **Immediate (type I)**
- **Antibody-mediated (type II)**
- **Immune complex–mediated (type III)**
- **Delayed-type Hypersensitivity (type IV)**
- **Type V Thyrotoxicosis, Myasthenia gravis.**

Hypersensitivity Reactions

Type I Over view

Type of Hypersensitivity	Immune Mechanisms	Mechanisms of Tissue Injury
Immediate (type I)	Activation of Th2 cells resulting in the production of IgE which in turn binds to FcεR on mast cells, basophils and eosinophils	**Immediate reaction** • Degranulation and release of vasoactive amines (ie. histamine) and proteases **Late-phase reaction** • Synthesis and secretion of prostaglandins and leukotrienes • Cytokine-induced inflammation and leukocyte recruitment

Hypersensitivity Reactions

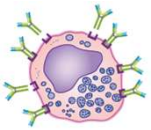
TYPE I (IMMEDIATE) HYPERSENSITIVITY

Type I is the only type of hypersensitivity mediated by IgE antibodies and mast cells. It is manifested within minutes of the re-exposure to an antigen. The IgE response is the normal protective response against many metazoan parasites, which are too large to be phagocytized or killed by other cytopathic mechanisms. Approximately 20% of all individuals in the United States, however, display this immune response against harmless environmental antigens, such as pet dander or pollen; these responses are called **atopic** or **allergic** responses.

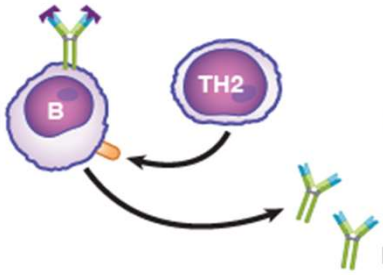
Hypersensitivity Reactions

Type I

1 First exposure to allergen



3 B cell produces IgE immunoglobulin; it attaches to Fc receptor on mast cell



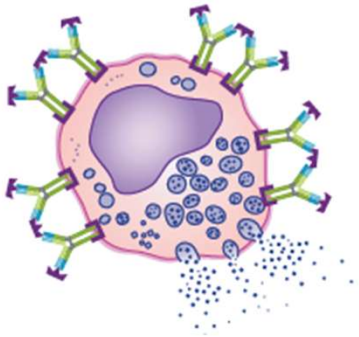
2 TH2 release of IL-4 and IL-13 stimulates B cell to produce IgE; class switching occurs

IgE Antibody

Hypersensitivity Reactions

TYpE I

4 Second exposure to allergen

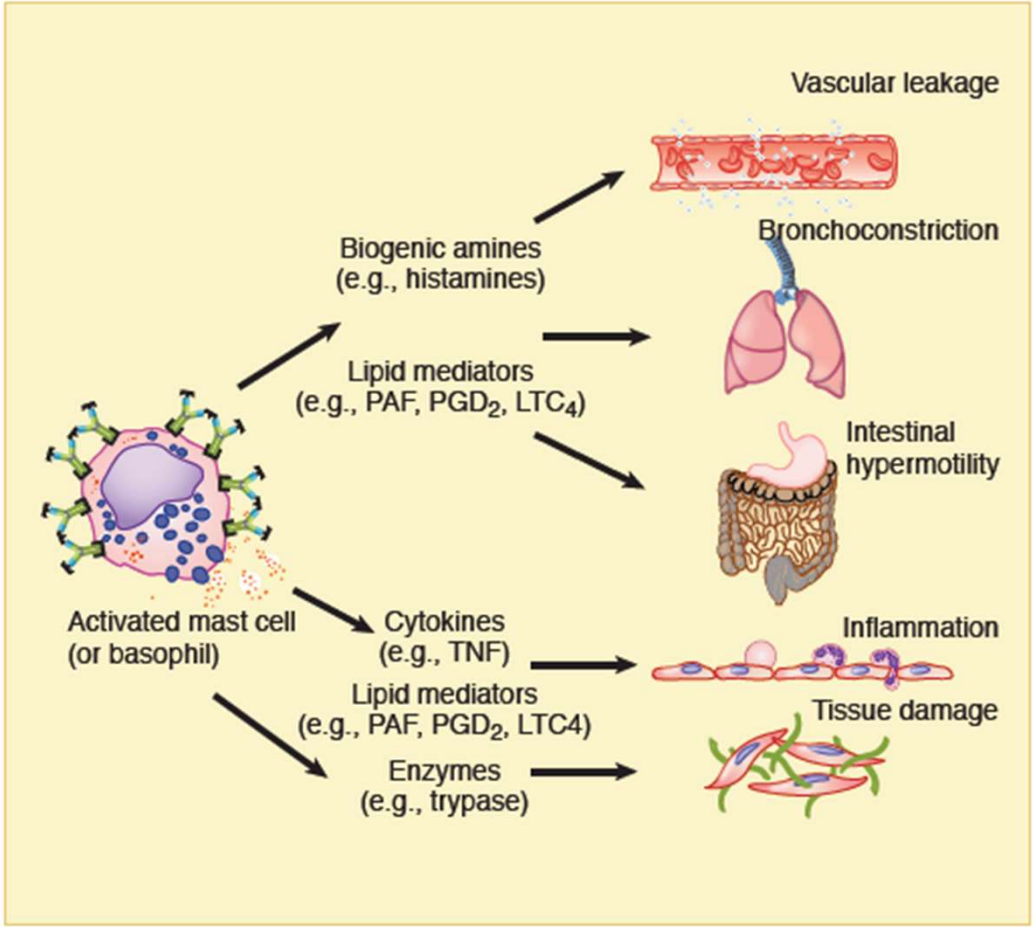


5 Allergen cross-links several IgE molecules on mast cell and cell degranulates, releasing powerful chemicals

Hypersensitivity Reactions

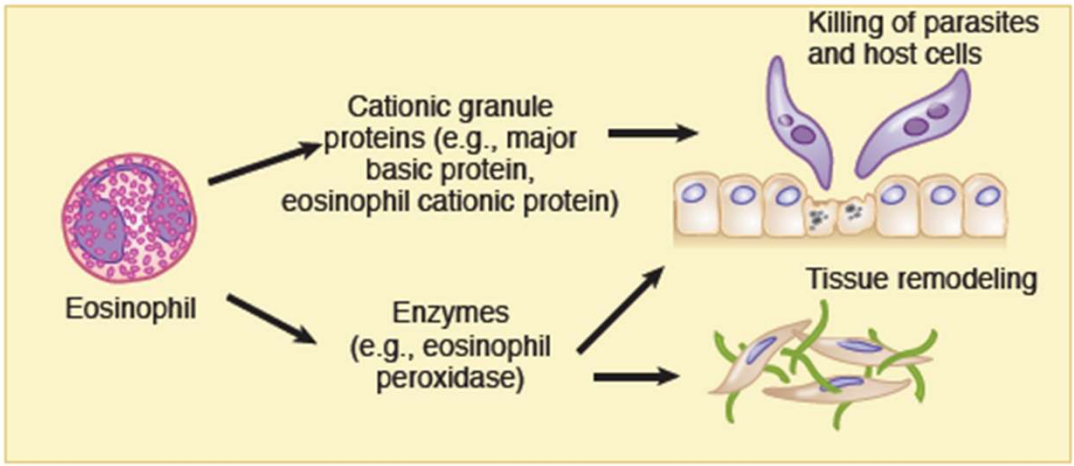
Type I

The effector cells of the immediate hypersensitivity reaction are mast cells, basophils, and eosinophils. The soluble substances they release into the site cause the symptoms of the reaction. Approximately 2-4 hours after the immediate response to release of these mediators, a **late-phase reaction** is mediated by products of the arachidonic acid cascade.



Hypersensitivity Reactions

Type I



Hypersensitivity Reactions

Mass cell mediators

Mediators Stored and Released	Effect
Histamine	Smooth muscle contraction; increased vascular permeability
Heparin	Anticoagulant
Eosinophil chemotactic factor A (multiple chemokines)	Chemotactic
Mediators Newly Synthesized from Arachidonic Acid	**Effect**
Prostaglandin D_2, E_2, $F_{2\alpha}$	Increased smooth muscle contraction and vascular permeability
Leukotrienes C_4, D_4, E_4 (lipoxygenase pathway)	Increased smooth muscle contraction and vascular permeability
Leukotriene B_4	Chemotactic for neutrophils

Hypersensitivity Reactions

Allergic Diseases Due to Specific Allergens and Their Clinical Manifestations

Allergic Disease	Allergens	Clinical Findings
Allergic rhinitis (hay fever)	Trees, grasses, dust, cats, dogs, mites	Edema, irritation, mucus in nasal mucosa
Systemic anaphylaxis	**Insect stings, drug reactions**	Bronchial and tracheal constriction, complete vasodilation and death
Food allergies	Milk, eggs, fish, ereals, grains	Hives and gastrointestinal problems
Wheal and fla e	In vivo skin testing for allergies	Local skin edema, reddening, vasodilation of vessels
Asthma	Inhaled materials	Bronchial and tracheal constriction, edema, mucus production, massive inflam ation

Hypersensitivity Reactions

TYPE II (ANTIBODY-MEDIATED) HYPERSENSITIVITY

Antibodies against cell surface or extracellular matrix antigens cause diseases thatare **specific to the tissues** where those antigens are present; they are not usually systemic. In most cases, these antibodies are **autoantibodies**, but they may be produced against a foreign antigen that is cross-reactive with self-components of tissues.

Hypersensitivity Reactions

Continued.. Type II

These antibodies can cause tissue damage by 3 main mechanisms:

- Opsonization of cells
- Activation of the complement system which recruit neutrophils and macrophages that cause tissue damage
- Possible binding to normal cellular receptors and interference with their function In some types of type II hypersensitivity, complement is activated and/or ADCC is active (e.g., hemolytic disease of the newborn [HDNB]). In other types, cell function is altered in the absence of complement activation and ADCC (e.g., myasthenia gravis and Graves disease). Eventually, as these diseases progress, complexes of antigen and antibody may cause localized damage, but they **do not circulate** so the damage is localized to the specific issue.

Hypersensitivity Reactions

Cytotoxic Types

Disease	Target Antigen	Mechanism of Pathogenesis	Clinical Manifestations
Autoimmune hemolytic anemia (HDNB)	RBC membrane proteins (Rh, I Ags)	Opsonization, phagocytosis, and complement-mediated destruction of RBCs	Hemolysis, anemia
Acute rheumatic fever	Streptococcal cell-wall Ag; Ab cross-reacts with myocardial Ag	Inflammation, macrophage activation	Myocarditis, arthritis
Goodpasture syndrome	Type IV collagen in basement membranes of kidney glomeruli and lung alveoli	Complement- and Fc receptor–mediated inflammation	Nephritis, lung hemorrhage, linear Ab deposits
Transfusion reaction	ABO blood glycoproteins	IgM isohemagglutinins formed naturally in response to normal bacterial flo a cause opsonization +	Hemolysis

Hypersensitivity Reactions

Non-Cytotoxic types

Non-cytotoxic			
Myasthenia gravis	**Acetylcholine receptor**	Ab inhibits acetylcholine binding, downmodulates receptors	**Muscle weakness, paralysis**
Graves disease	**TSH receptor**	Ab-mediated stimulation of TSH receptors	**Hyperthyroidism followed by hypothyroidism**
Type II (insulin-resistant) diabetes	Insulin receptor	Ab inhibits binding of insulin	Hyperglycemia
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor, decreased absorption of vitamin B12	Abnormal erythropoiesis, anemia

Hypersensitivity Reactions

Type II Hypersensitivity : Example

An important example of type II hypersensitivity is **HDNB**, also known as erythroblastosis fetalis. In the foetus, this disease is due to transport of IgG specific for one of the Rhesus (Rh) protein antigens (RhD) across the placenta. About 85% of people are Rh+. If a pregnant woman is Rh– and the father is Rh+, there is a chance that the fetus will also be Rh+. Th s situation will pose no problem in the first pregnancy, as the mother's immune system will not usually encounter fetal blood cell antigens until placental separation at the time of birth. At that time, however, Rh+ fetal red blood cells will enter the maternal circulation and stimulate a T-dependent immune response, eventually resulting in the generation of memory B cells capable of producing IgG antibody against RhD. In a subsequent pregnancy with another Rh+ fetus, this maternal IgG can be transported across the placenta, react with fetal Rh+ red cells, and activate complement, producing hemolytic disease. Haemolytic disease of the new-born can be prevented by treating the Rh– mother with RhoGAM, a preparation of human anti-RhD antibody, at 28 weeks of gestation and again within 72 hours after birth. Th s antibody effectively eliminates the fetal Rh+ cells before they can generate RhD-specific memory B cells in the mother. Anti-RhD antibody should be given to and Rh– individual following any termination of pregnancy.

Hypersensitivity Reactions

TYPE III (IMMUNE COMPLEX) HYPERSENSITIVITY

The immune complexes that cause disease may involve either self or foreign antigens bound to antibodies. These immune complexes are filtered out of the circulation in the small vasculature, so their sites of ultimate damage do not reflect their sites of origin. These diseases tend to be systemic, with little tissue or organ specificity.

Hypersensitivity Reactions

Type III Hypersensitivity

Disease	Antigen Involved	Clinical Manifestations
Systemic lupus erythematosus+	**dsDNA**, Sm, other nucleoproteins	Nephritis, arthritis, vasculitis, **butterfl facial rash**
Poststreptococcal glomerulonephritis	Streptococcal cell wall Ags (may be "planted" in glomerular basement membrane)	Nephritis, **"lumpy-bumpy" deposits**
Arthus reaction	Any injected protein	Local pain and edema
Serum sickness	Various proteins	Arthritis, vasculitis, nephritis
Polyarteritis nodosa	Hepatitis B virus Ag	Systemic vasculitis

+Other autoimmune diseases correlated with production of antinuclear antibodies include diffuse systemic sclerosis (antibodies to DNA topoisomerase 1), limited scleroderma (CREST; antibodies to centromeric proteins) and Sjögren syndrome (antibodies to ribonucleoproteins).

Hypersensitivity Reactions

TYPE IV (T-CELL–MEDIATED) HYPERSENSITIVITY

T-lymphocytes may cause tissue injury by triggering delayed-type hypersensitivity (DTH) reactions or by directly killing target cells. These reactions are elicited by CD4+ Th1, Th17 cells, or CD8+ CTLs, which activate macrophages, recruit neutrophils, and induce inflammation. These T cells may be autoreactive or specific. against foreign protein antigens bound to tissues. T-cell-mediated tissue injury is common during the protective immune response against persistent intracellular microbes.

Hypersensitivity Reactions

Type IV Example

Disease	Specifi ity of Pathogenic T Cells	Clinical Manifestations
Tuberculin test	PPD (tuberculin & mycolic acid)	Indurated skin lesion (granuloma)
Contact dermatitis	**Nickel, poison ivy/oak catechols, hapten/carrier**	Vesicular skin lesions, pruritus, rash
Hashimoto thyroiditis*	Unknown Ag in thyroid	**Hypothyroidism**
Multiple sclerosis	Myelin Basic Protein	Progressive demyelination, blurred vision, paralysis
Rheumatoid arthritis*	Unknown Ag in joint synovium (type II collagen?)	Rheumatoid factor (IgM against Fc region of IgG), alpha-cyclic citrullinated peptide (α-CCP) antibodies, chronic arthritis, inflam ation, destruction of articular cartilage and bone
Insulin-dependent diabetes mellitus (type I)*	Islet-cell antigens, insulin, glutamic acid decarboxylase, others	Chronic inflam ation and destruction of β cells, polydipsia, polyuria, polyphagia, ketoacidosis

Hypersensitivity Reactions

Type IV Examples

Disease	Specifi ity of Pathogenic T Cells	Clinical Manifestations
Insulin-dependent diabe-tes mellitus (type I)*	Islet-cell antigens, insulin, glutamic acid decarbox-ylase, others	Chronic inflam ation and destruction of β cells, polydipsia, polyuria, polyphagia, ketoacidosis
Guillain-Barré syndrome*	Peripheral nerve myelin or gangliosides	Ascending paralysis, peripheral nerve demyelination
Celiac disease	CD4+ cells—gliadin, CD8+ cells—HLA class I-like molecule expressed during stress	Gluten-sensitive enteropathy
Crohn disease	Unknown Ag, commensal bacteria?	Chronic intestinal inflam ation due to Th1 and Th17 cells, obstruction

*Diseases classified a type IV pathologies in which autoantibodies are present and used as clinical markers

Hypersensitivity Reactions

THE PATHOGENESIS OF AUTOIMMUNITY

The key factor in the development of autoimmunity is the recognition of self antigens by autoreactive lymphocytes, which then become activated, proliferate, and differentiate to produce effector cells and cytokines that cause tissue injury. Autoimmunity must initially result from a failure of mechanisms of **central tolerance,** as cells are “educated” in the bone marrow and thymus (*see* chapter 3). Self-reactive lymphocytes that escaped central tolerance are subject to the different mechanisms of peripheral tolerance. The 3 primary mechanisms that induce peripheral tolerance are anergy, deletion and suppression B lymphocytes that recognize self-antigen in the absence of the T-cell signalling become anergic and express high levels of IgD on their surface, excluding them from secondary lymphoid tissues. Anergic B lymphocytes are then unable to receive the signals necessary for survival and undergo apoptosis. Additionally, B lymphocytes have inhibitory receptors that can be engaged when self-antigen is recognized suppressing their activity.

Hypersensitivity Reactions

Autoimmune Disease- Pathogenesis..

Like self-reactive B lymphocytes, T lymphocytes that recognize self-antigen in the absence of the appropriate costimulatory signals are subject to anergy or deletion. Anergy is the result of a breakdown in either TCR signalling or the binding of an inhibitory receptor, CTLA-4 or PD-1. Deletion of self-reactive T lymphocytes is due to apoptosis by activation of the caspase signaling pathway or the Fas signaling pathway. Self-reactive T lymphocytes are also subject to suppression by Tregs. Although a majority of Tregs are generated during central tolerance, some arise in the periphery. Tregs secrete IL-10 and TGF-beta that inhibit the activation of lymphocytes, macrophage and dendritic cells. CTLA-4 is expressed at high levels on Tregs and is thought to bind to and sequester the costimulatory molecule B7 which would otherwise be used to activate T lymphocytes.

Development of autoimmune disease is due to a combination of genetic and environmental factors as well as hormonal triggers. Among the strongest genetic associations with the development of autoimmune disease are the **HLA genes**. Also known to contribute to autoimmunity are polymorphisms in non-HLA genes.

Infections and tissue injury may alter the way that self-antigens are presented to lymphocytes and serve as an inciting factor in the development of disease. Because autoimmune reactions against one self-antigen may injure other tissues and expose other potential self-antigens for recognition, autoimmune diseases tend to be chronic and progressive.

Hypersensitivity Reactions

Examples of HLA linked autoimmuno disease

Disease	HLA Allele
Rheumatoid arthritis	DR4
Insulin-dependent diabetes mellitus	DR3/DR4
Multiple sclerosis, Goodpasture's	DR2
Systemic lupus erythematosus	DR2/DR3
Ankylosing spondylitis, psoriasis, inflam atory bowel disease, reactive arthritis	B27
Celiac disease	DQ2 or DQ8
Graves disease	B8

Hypersensitivity Reactions

Chapter Summary

- There are 4 types of hypersensitivity:
  - Immediate
  - Antibody-mediated (cytotoxic, blocking, enhancing)
  - Immune complex-mediated
  - T cell-mediated
- Hypersensitivity reactions require initial sensitization, and subsequent exposures to the same or cross-reactive antigens cause the damage.

Hypersensitivity Reactions

Chapter Summary

Type I hypersensitivities (immediate) involve IgE antibodies and mast cells, show symptoms in minutes, and are mounted against harmless environmental antigens in atopic or allergic individuals.

— Initial tissue damage in immediate hypersensitivities is due to release of mast cell mediators, and late-phase reactions involve products of the arachidonic acid cascade.

— Examples include hay fever, asthma, food allergies, and systemic anaphylaxis.

Hypersensitivity Reactions

Chapter Summary

• **Type II (antibody-mediated) hypersensitivities** are tissue-specific and involve autoantibodies that opsonize or activate complement. Some noncytotoxic forms (myasthenia gravis, Graves disease, type II diabetes) cause interference with cellular function.

— Examples (cytotoxic) include autoimmune hemolytic anemia, hemolytic disease of the new-born, autoimmune thrombocytopenic purpura, Goodpasture syndrome, rheumatic fever, and pernicious anemia.

Hypersensitivity Reactions

Chapter Summary

• Type III (immune complex) hypersensitivities cause systemic damage by activating complement wherever immune complexes of antibodies against self or foreign antigens are filtered from the circulation. — Examples include systemic lupus erythematosus, polyarteritis nodosa, poststreptococcal glomerulonephritis, serum sickness, and the Arthus reaction.

Hypersensitivity Reactions

• Type IV hypersensitivities are delayed-type (manifesting symptoms 48-72 hrs after reexposure); are caused by TH1 and TH17 cells, CD8+ cells, and macrophages; and are common results of infection with persistent intracellular microbes.

— Examples include the tuberculin test, insulin-dependent diabetes mellitus, celiac disease, contact dermatitis, Guillain-Barré syndrome, RA, Crohn disease and Hashimoto thyroiditis.

• Autoimmune diseases may associate with specific class II MHC haplotypes, envi-ronmental factors, hormonal factors, or be triggered by infections.


Hypersensitivity
Reactions
The End