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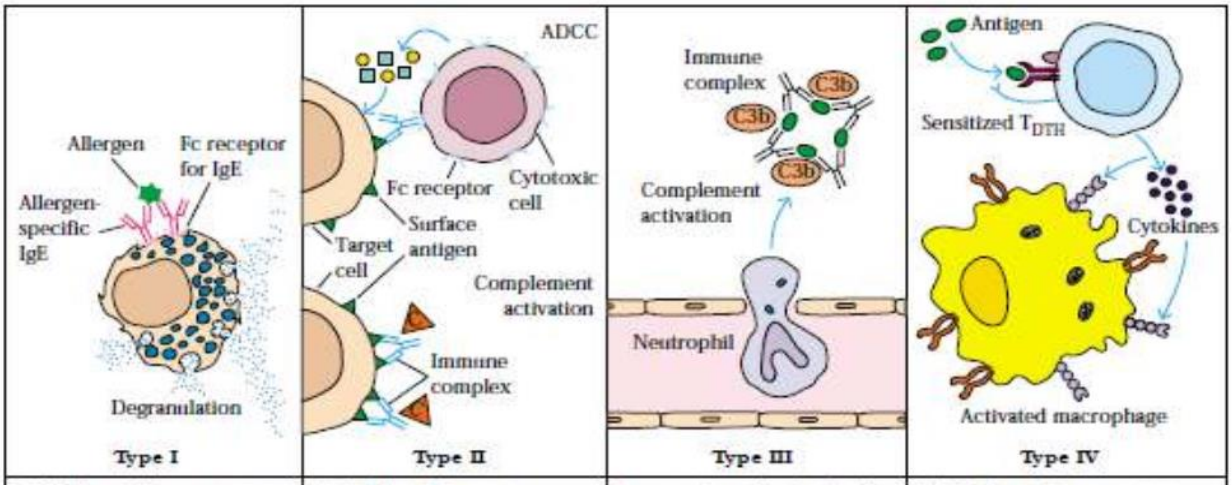
LECTURE 08: IMMUNE RESPONSES

An immune response mobilizes a battery of effector molecules that act to remove antigen by various mechanisms. Generally, these effector molecules induce a localized inflammatory response that eliminates antigen without extensively damaging the host's tissue. Under certain circumstances, however, this inflammatory response can have deleterious effects, resulting in significant tissue damage or even death. This inappropriate immune response is termed **hypersensitivity** or **allergy.** Although the word *hypersensitivity* implies an increased response, the response is not always heightened but may, instead, be an inappropriate immune response to an antigen. Hypersensitive reactions may develop in the course of either humoral or cell-mediated responses.

Anaphylactic reactions within the humoral branch are initiated by antibody or antigen-antibody complexes as **immediate hypersensitivity,** because the symptoms are manifest within minutes or hours after a sensitized recipient encounters antigen. **Delayed-type hypersensitivity (DTH)** is so named in recognition of the delay of symptoms until days after exposure.

Gell and Coombs Classification



Type I	Type II	Type III	Type IV
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune-Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils	Sensitized T_H1 cells release cytokines that activate macrophages or T_C cells which mediate direct cellular damage
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulnephritis, rheumatoid arthritis, and systemic lupus erythematosus	Typical manifestations include contact dermatitis, tubercular lesions and graft rejection

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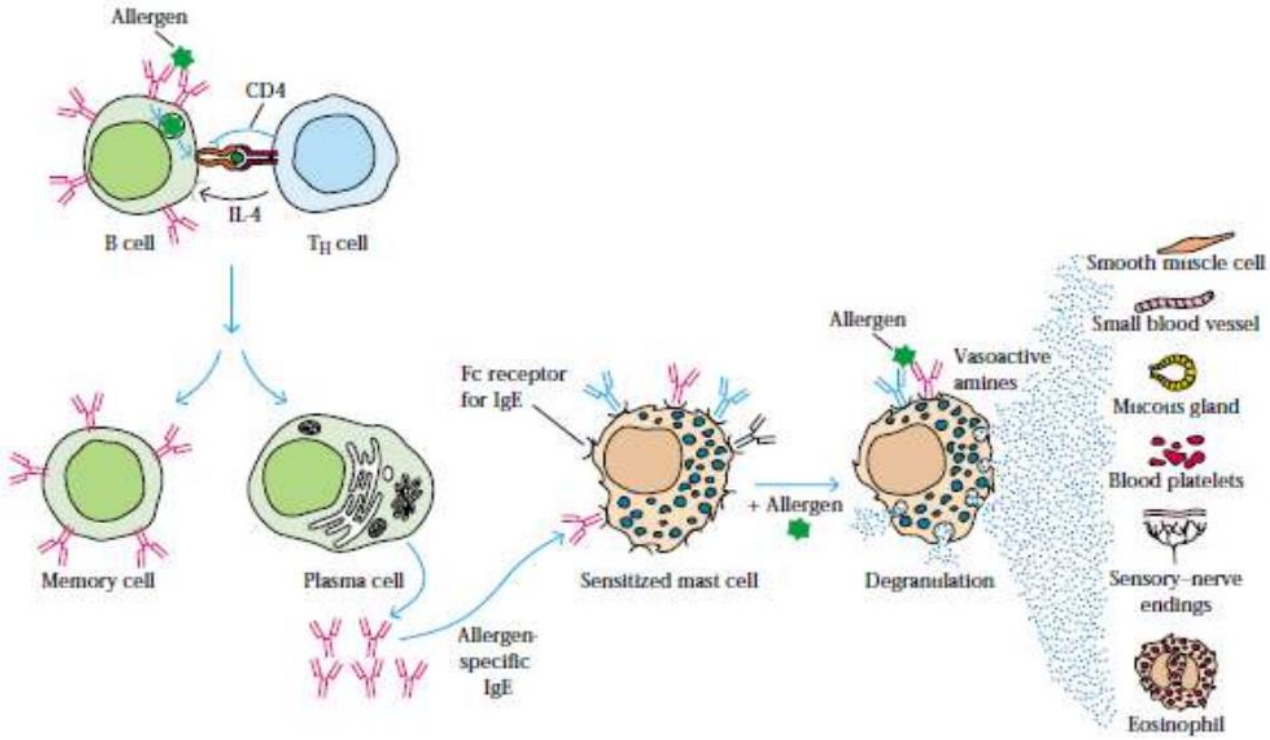
Several forms of hypersensitive reaction can be distinguished, reflecting differences in the effector molecules generated in the course of the reaction. In immediate hypersensitive reactions, different antibody isotypes induce different immune effector molecules. IgE antibodies, for example, induce mast-cell degranulation with release of histamine and other biologically active molecules. IgG and IgM antibodies, on the other hand, induce hypersensitive reactions by activating complement. The effector molecules in the complement reactions are the membrane-attack complex and such complement split products as C3a, C4a, and C5a. In delayed-type hypersensitivity reactions, the effector molecules are various cytokines secreted by activated T_H or T_C cells.

IgE-Mediated (Type I) Hypersensitivity

A type I hypersensitive reaction is induced by certain types of antigens referred to as **allergens,** and has all the hallmarks of a normal humoral response. That is, an allergen induces a humoral antibody response by the same mechanisms as described in Chapter 11 for other soluble antigens, resulting in the generation of antibody-secreting plasma cells and memory cells. What distinguishes a type I hypersensitive response from a normal humoral response is that the plasma cells secrete IgE. This class of antibody binds with high affinity to **Fc receptors** on the surface of tissue mast cells and blood basophils. Mast cells and basophils coated by IgE are said to be sensitized. A later exposure to the same allergen cross-links the membrane-bound IgE on sensitized mast cells and basophils, causing **degranulation** of these cells (see Figure).



The pharmacologically active mediators released from the granules act on the surrounding tissues. The principal effects—vasodilation and smooth-muscle contraction—may be either systemic or localized, depending on the extent of mediator release.

There Are Several Components of Type I Reactions

Allergens

The majority of humans mount significant IgE responses only as a defense against parasitic infections. After an individual has been exposed to a parasite, serum IgE levels increase and remain high until the parasite is successfully cleared from the body. Some persons, however, may have an abnormality called **atopy,** a hereditary predisposition to the development of immediate hypersensitivity reactions against common environmental antigens. The IgE regulatory defects suffered by atopic individuals allow nonparasitic antigens to stimulate inappropriate IgE production, leading to tissuedamaging type I hypersensitivity. The term *allergen* refers specifically to nonparasitic antigens capable of stimulating type I hypersensitive responses in allergic individuals.

The abnormal IgE response of atopic individuals is at least partly genetic—it often runs in families.Atopic individuals have abnormally high levels of circulating IgE and also more than normal numbers of circulating eosinophils. These individuals are more susceptible to allergies such as hay fever, eczema, and asthma. The genetic propensity to atopic responses has been mapped to several candidate loci. One locus, on chromosome 5q, is linked to a region that encodes a variety of cytokines, including IL-3, IL-4, IL-5, IL-9, IL-13, and GM-CSF. A second locus, on chromosome 11q,is linked to a region that encodes the _ chain of the high-affinity IgE receptor. It is known that inherited atopy is multigenic and that other loci probably also are involved. Indeed, as information from the Human Genome Project is analyzed, other candidate genes may be revealed.

Most allergic IgE responses occur on mucous membrane surfaces in response to allergens that enter the body by either inhalation or ingestion. Of the common allergens listed in Table, few have been purified and characterized. Those that have include the allergens from rye grass pollen, ragweed pollen, codfish, birch pollen, timothy grass pollen, and bee venom. Each of these allergens has been shown to be a multiantigenic system that contains a number of allergenic components. Ragweed pollen, a major allergen in the United States, is a case in point. It has been reported that a square mile of ragweed yields 16 tons of pollen in a single season. Indeed, all regions of the United States are plagued by ragweed pollen as well as pollen from trees indigenous to the region. The pollen particles are inhaled, and their tough outer wall is dissolved by enzymes in the mucous

secretions, releasing the allergenic substances. Chemical fractionation of ragweed has revealed a variety of substances, most of which are not allergenic but are capable of eliciting an IgM or IgG response. Of the five fractions that are allergenic (i.e., able to induce an IgE response), two evoke allergenic reactions in about 95% of ragweed-sensitive individuals and are called major allergens; these are designated the E and K fractions. The other three, called Ra3, Ra4, and Ra5, are minor allergens that induce an allergic response in only 20% to 30% of sensitive subjects.

- Proteins
  - Foreign serum
  - Vaccines
- Plant pollens
  - Rye grass
  - Ragweed
  - Timothy grass
  - Birch trees
- Drugs
  - Penicillin
  - Sulfonamides
  - Local anesthetics
  - Salicylates
- Foods
  - Nuts
  - Seafood
  - Eggs
  - Peas, beans
  - Milk
- Insect products
  - Bee venom
  - Wasp venom
  - Ant venom
  - Cockroach calyx
  - Dust mites
- Mold spores
- Animal hair and dander

Why are some pollens (e.g., ragweed) highly allergenic, whereas other equally abundant pollens (e.g., nettle) are rarely allergenic? No single physicochemical property seems to distinguish the highly allergenic E and K fractions of ragweed from the less allergenic Ra3, Ra4, and Ra5 fractions and from the nonallergenic fractions. Rather, allergens as a group appear to possess diverse properties. Some allergens, including foreign serum and egg albumin, are potent antigens; others, such as plant pollens, are weak antigens. Although most allergens are small proteins or protein-bound substances having a molecular weight between 15,000 and 40,000, attempts to identify some common chemical property of these antigens have failed. It appears that allergenicity is a consequence of a complex series of interactions involving not only the allergen but also the dose, the sensitizing route, sometimes an adjuvant, and—most important, as noted above— the genetic constitution of the recipient.

Serum IgE

Serum IgE levels in normal individuals fall within the range of 0.1–0.4 μg/ml; even the most severely allergic individuals rarely have IgE levels greater than 1 μg/ml. These low levels made physiochemical studies of IgE difficult; it was not until the discovery of an IgE myeloma by S. G.

O. Johansson and H. Bennich in 1967 that extensive chemical analysis of IgE could be undertaken. IgE was found to be composed of two heavy ε and two light chains with a combined molecular weight of 190,000. The higher molecular weight as compared with IgG (150,000) is due to the presence of an additional constant-region domain. This additional domain (C_H4) contributes to an altered conformation of the Fc portion of the molecule that enables it to bind to glycoprotein receptors on the surface of basophils and mast cells. Although the half-life of IgE in the serum is only 2–3 days, once IgE has been bound to its receptor on mast cells and basophils, it is stable in that state for a number of weeks.

Mast Cells and Basophils

The cells that bind IgE were identified by incubating human leukocytes and tissue cells with either ^{125}I-labeled IgE myeloma protein or ^{125}I-labeled anti-IgE. In both cases, autoradiography revealed that the labeled probe bound with high affinity to blood basophils and tissue mast cells. Basophils are granulocytes that circulate in the blood of most vertebrates; in humans, they account for 0.5%–1.0% of the circulating white blood cells. Their granulated cytoplasm stains with basic dyes, hence the name basophil. Electron microscopy reveals a multilobed nucleus, few mitochondria, numerous glycogen granules, and electron-dense membrane-bound granules scattered throughout the cytoplasm that contain pharmacologically active mediators.

Mast-cell precursors are formed in the bone marrow during hematopoiesis and are carried to virtually all vascularized peripheral tissues, where they differentiate into mature cells. Mast cells are found throughout connective tissue, particularly near blood and lymphatic vessels. Some tissues, including the skin and mucous membrane surfaces of the respiratory and gastrointestinal tracts, contain high concentrations of mast cells; skin, for example, contains 10,000 mast cells per mm3. Electron micrographs of mast cells reveal numerous membrane-bounded granules distributed throughout the cytoplasm, which, like those in basophils, contain pharmacologically active mediators.After activation, these mediators are released from the granules, resulting in the clinical manifestations of the type I hypersensitive reaction.

Mast cell populations in different anatomic sites differ significantly in the types and amounts of allergic mediators they contain and in their sensitivity to activating stimuli and cytokines. Mast cells also secrete a large variety of cytokines that affect a broad spectrum of physiologic, immunologic, and pathologic processes.

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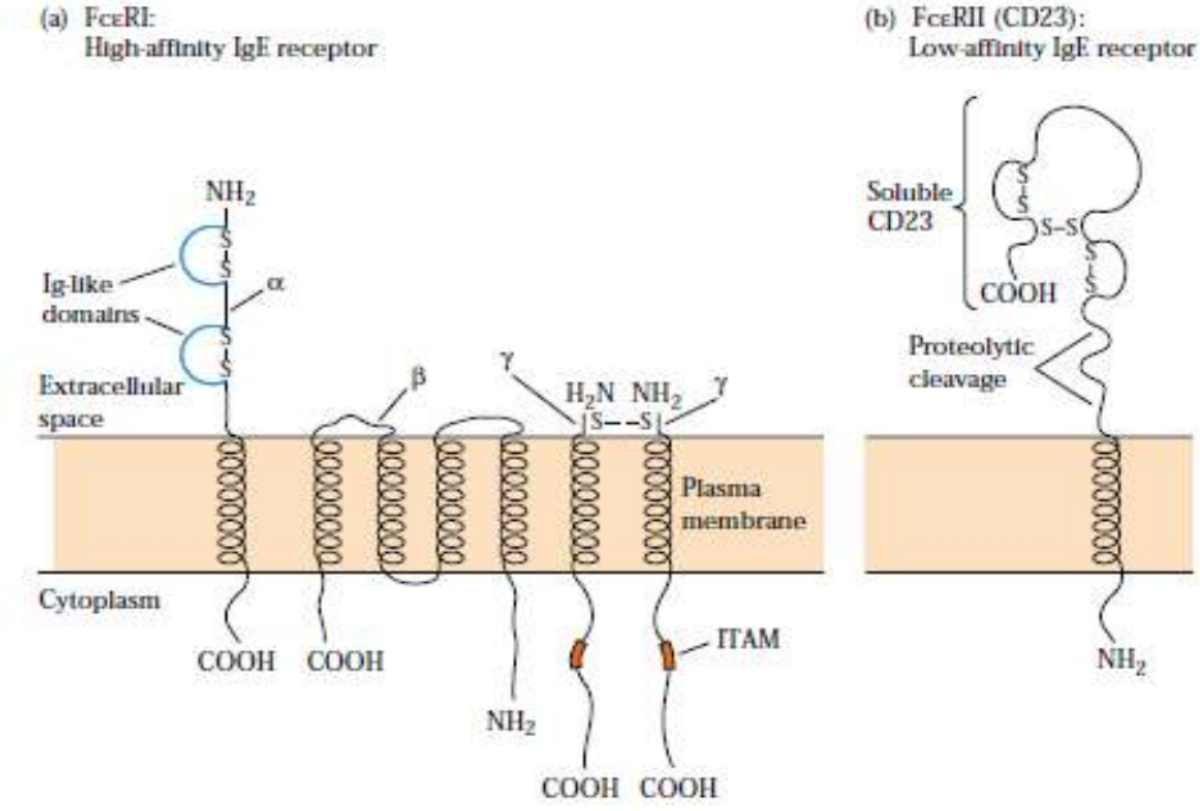
IgE-Binding Fc Receptors

The reaginic activity of IgE depends on its ability to bind to a receptor specific for the Fc region of the ε heavy chain. Two classes of FcεR been identified, designated FcεRI and FcεRII, which are expressed by different cell types and differ by 1000- fold in their affinity for IgE.

High-Affinity Receptor (FcεRI)

Mast cells and basophils express FcεRI, which binds IgE with a high affinity (K_D = 1–2 X 10^{-9} M). The high affinity of this receptor enables it to bind IgE despite the low serum concentration of IgE (1 X10^{-7}). Between 40,000 and 90,000 FcεRI molecules have been shown to be present on a human basophil.

The FcεRI receptor contains four polypeptide chains: an α and a β chain and two identical disulfide-linked γ chains. The external region of the α chain contains two domains of 90 amino acids that are homologous with the immunoglobulin-fold structure, placing the molecule in the immunoglobulin superfamily (see Figure).



FcεRI interacts with the C_H3/C_H3 and C_H4/C_H4 domains of the IgE molecule via the two Ig-like domains of the α chain. The β chain spans the plasma membrane four times and is thought to

link the α chain to the γ homodimer. The disulfide-linked γ chains extend a considerable distance into the cytoplasm. Each γ chain has a conserved sequence in its cytosolic domain known as an immunoreceptor tyrosine-based activation motif (ITAM). As described earlier, two other membrane receptors that have this motif are CD3 and the associated ζ chains of the T-cell receptor complex and the Ig-α/Ig-β chains associated with membrane immunoglobulin on B cells.

The ITAM motif on these three receptors interacts with protein tyrosine kinases to transduce an activating signal to the cell. Allergen mediated crosslinkage of the bound IgE results in aggregation of the FcεRI receptors and rapid tyrosine phosphorylation, which initiates the process of mast-cell degranulation. The role of FcεRI in anaphylaxis is confirmed by experiments conducted in mice that lack FcεRI. These mice have normal levels of mast cells but are resistant to localized and systemic anaphylaxis.

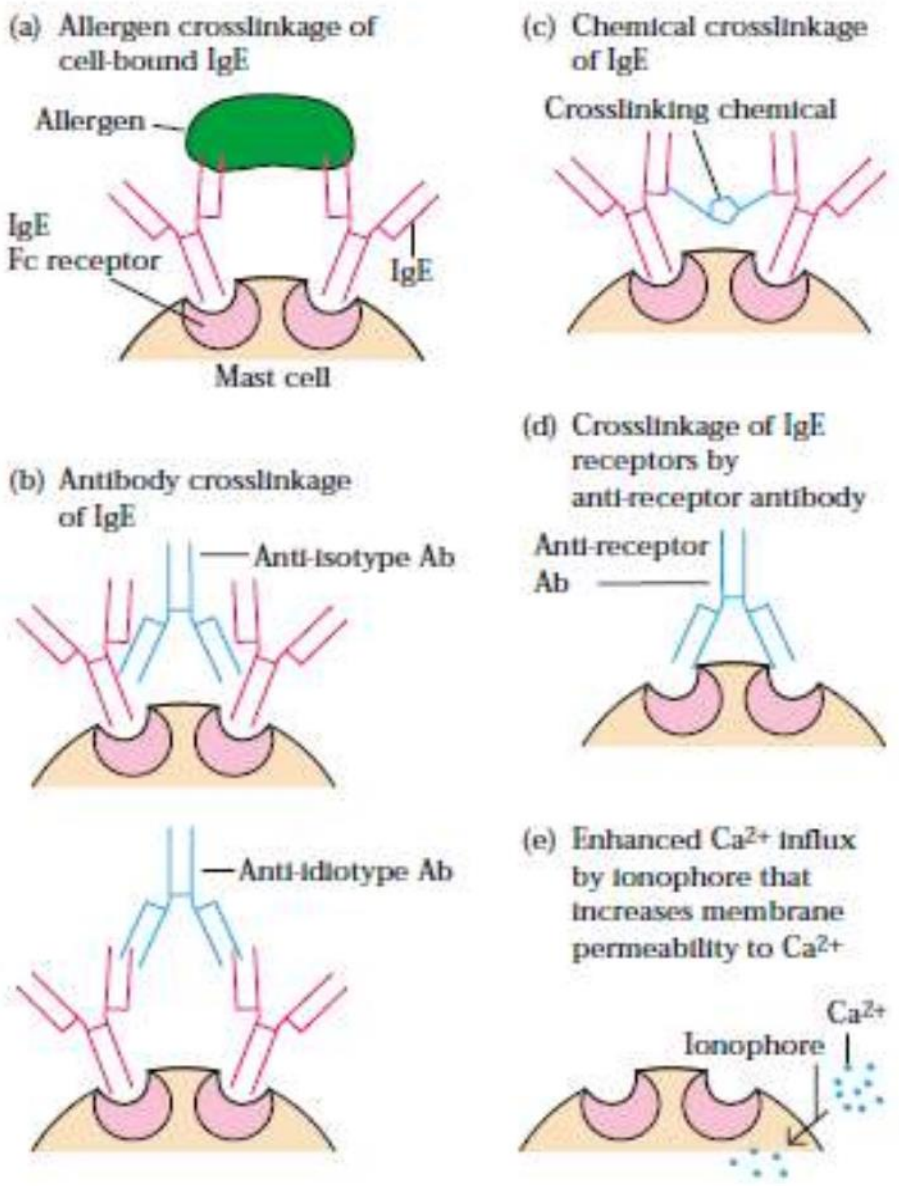
Low-Affinity Receptor (FcεRII)

The other IgE receptor, designated Fc_RII (or CD23), is specific for the C_H3/ C_H3 domain of IgE and has a lower affinity for IgE (KD = 1 X 10–6M) than does FcεRI (see Figure). The FcεRII receptor appears to play a variety of roles in regulating the intensity of the IgE response. Allergen crosslinkage of IgE bound to FcεRII has been shown to activate B cells, alveolar macrophages, and eosinophils. When this receptor is blocked with monoclonal antibodies, IgE secretion by B cells is diminished. A soluble form of FcεRII (or sCD23), which is generated by autoproteolysis of the membrane receptor, has been shown to enhance IgE production by B cells. Interestingly, atopic individuals have higher levels of CD23 on their lymphocytes and macrophages and higher levels of sCD23 in their serum than do nonatopic individuals.

Receptor crosslinkage

IgE-mediated degranulation begins when an allergen crosslinks IgE that is bound (fixed) to the Fc receptor on the surface of a mast cell or basophil. In itself, the binding of IgE to FcεRI apparently has no effect on a target cell. It is only after allergen crosslinks the fixed IgE-receptor complex that degranulation proceeds. The importance of crosslinkage is indicated by the inability of monovalent allergens, which cannot crosslink the fixed IgE, to trigger degranulation.

Experiments have revealed that the essential step in degranulation is crosslinkage of two or more FcεRI molecules— with or without bound IgE. Although crosslinkage is normally affected by the interaction of fixed IgE with divalent or multivalent allergen, it also can be affected by a variety of experimental means that bypass the need for allergen and in some cases even for IgE.



Schematic diagrams of mechanisms that can trigger degranulation of mast cells. Note that mechanisms (b) and (c) do not require allergen; mechanisms (d) and (e) require neither allergen nor IgE; and mechanism (e) does not even require receptor crosslinkage.

Intracellular Events Also Regulate Mast-Cell Degranulation

The cytoplasmic domains of the β and γ chains of FcεRI are associated with protein tyrosine kinases (PTKs). Crosslinkage of the FcεRI receptors activates the associated PTKs, resulting in the phosphorylation of tyrosines within the ITAMs of the γ subunit as well as phosphorylation of residues on the β subunit and on phospholipase C. These phosphorylation events induce the production of a number of second messengers that mediate the process of degranulation (see Figure).

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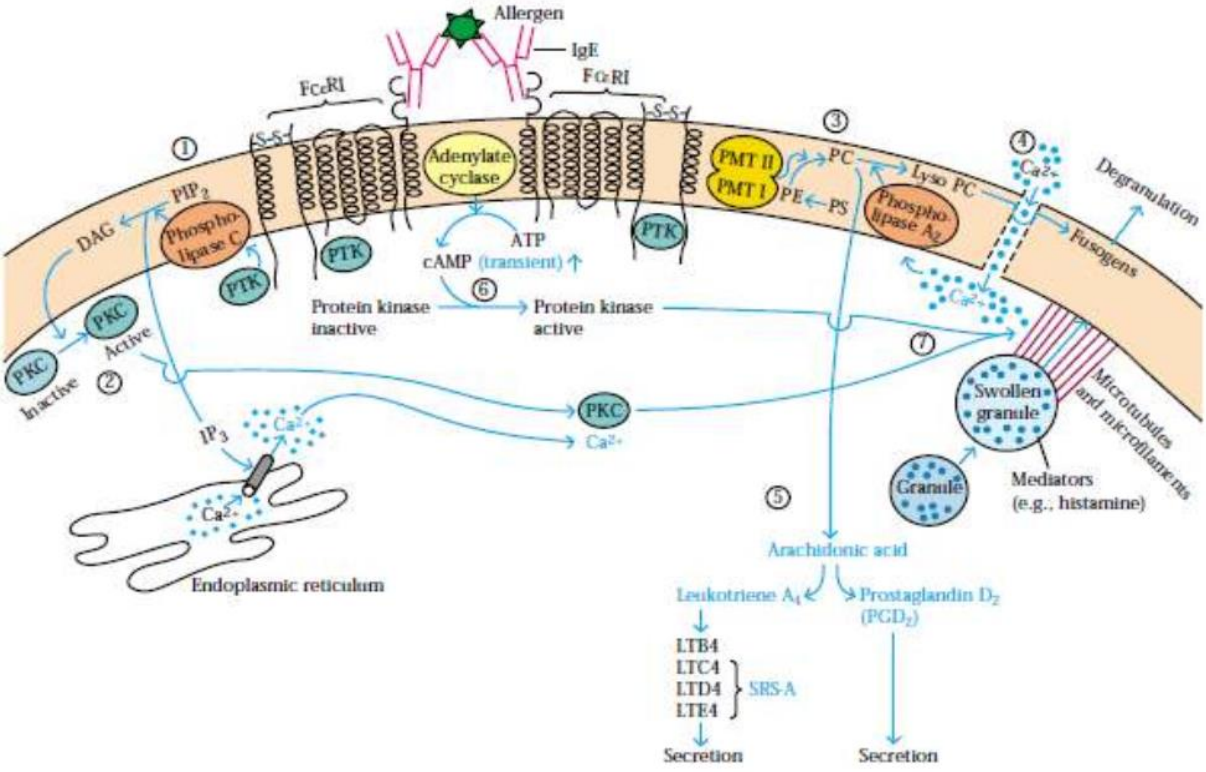

Within 15 s after crosslinkage of FcεRI, methylation of various membrane phospholipids is observed, resulting in an increase in membrane fluidity and the formation of Ca^{2+} channels. An increase of Ca^{2+} reaches a peak within 2 min of FcεRI crosslinkage.

This increase is due both to the uptake of extracellular Ca^{2+} and to a release of Ca^{2+} from intracellular stores in the endoplasmic reticulum. The Ca^{2+} increase eventually leads to the formation of arachidonic acid, which is converted into two classes of potent mediators: **prostaglandins** and **leukotrienes**. The increase of Ca^{2+} also promotes the assembly of microtubules and the contraction of microfilaments, both of which are necessary for the movement of granules to the plasma membrane. The importance of the Ca^{2+} increase in mast-cell degranulation is highlighted by the use of drugs, such as disodium cromoglycate (cromolyn sodium), that block this influx as a treatment for allergies.

Concomitant with phospholipid methylation and Ca^{2+} increase, there is a transient increase in the activity of membrane bound adenylate cyclase, with a rapid peak of its reaction product, cyclic adenosine monophosphate (cAMP), reached about 1 min after crosslinkage of FcεRI.The effects of cAMP are exerted through the activation of cAMP-dependent protein kinases, which phosphorylate proteins on the granule membrane, thereby changing the permeability of the granules

to water and Ca^{2+}. The consequent swelling of the granules facilitates their fusion with the plasma membrane, releasing their contents. The increase in cAMP is transient and is followed by a drop in cAMP to levels below baseline. This drop in cAMP appears to be necessary for degranulation to proceed; when cAMP levels are increased by certain drugs, the degranulation process is blocked. Several of these drugs are given to treat allergic disorders.

Principal mediators involved in Type – I Hypersensitive reaction

Mediator	Effects
PRIMARY	
Histamine, heparin	Increased vascular permeability; smooth-muscle contraction
Serotonin	Increased vascular permeability; smooth-muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A)	Neutrophil chemotaxis
Proteases	Bronchial mucus secretion; degradation of blood-vessel basement membrane; generation of complement split products
SECONDARY	
Platelet-activating factor	Platelet aggregation and degranulation; contraction of pulmonary smooth muscles
Leukotrienes (slow reactive substance of anaphylaxis, SRS-A)	Increased vascular permeability; contraction of pulmonary smooth muscles
Prostaglandins	Vasodilation; contraction of pulmonary smooth muscles; platelet aggregation
Bradykinin	Increased vascular permeability; smooth-muscle contraction
Cytokines	
IL-1 and TNF-α	Systemic anaphylaxis; increased expression of CAMs on venular endothelial cells
IL-2, IL-3, IL-4, IL-5, IL-6, TGF-β, and GM-CSF	Various effects (see Table 12-1)

Mechanism of action of some drugs used to treat Type – I Hypersensitive reaction

Drug	Action
Antihistamines	Block H_1 and H_2 receptors on target cells
Cromolyn sodium	Blocks Ca^{2+} influx into mast cells
Theophylline	Prolongs high cAMP levels in mast cells by inhibiting phosphodiesterase, which cleaves cAMP to 5'-AMP*
Epinephrine (adrenalin)	Stimulates cAMP production by binding to β-adrenergic receptors on mast cells*
Cortisone	Reduces histamine levels by blocking conversion of histidine to histamine and stimulates mast-cell production of cAMP*

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Antibody-Mediated Cytotoxic (Type II) Hypersensitivity

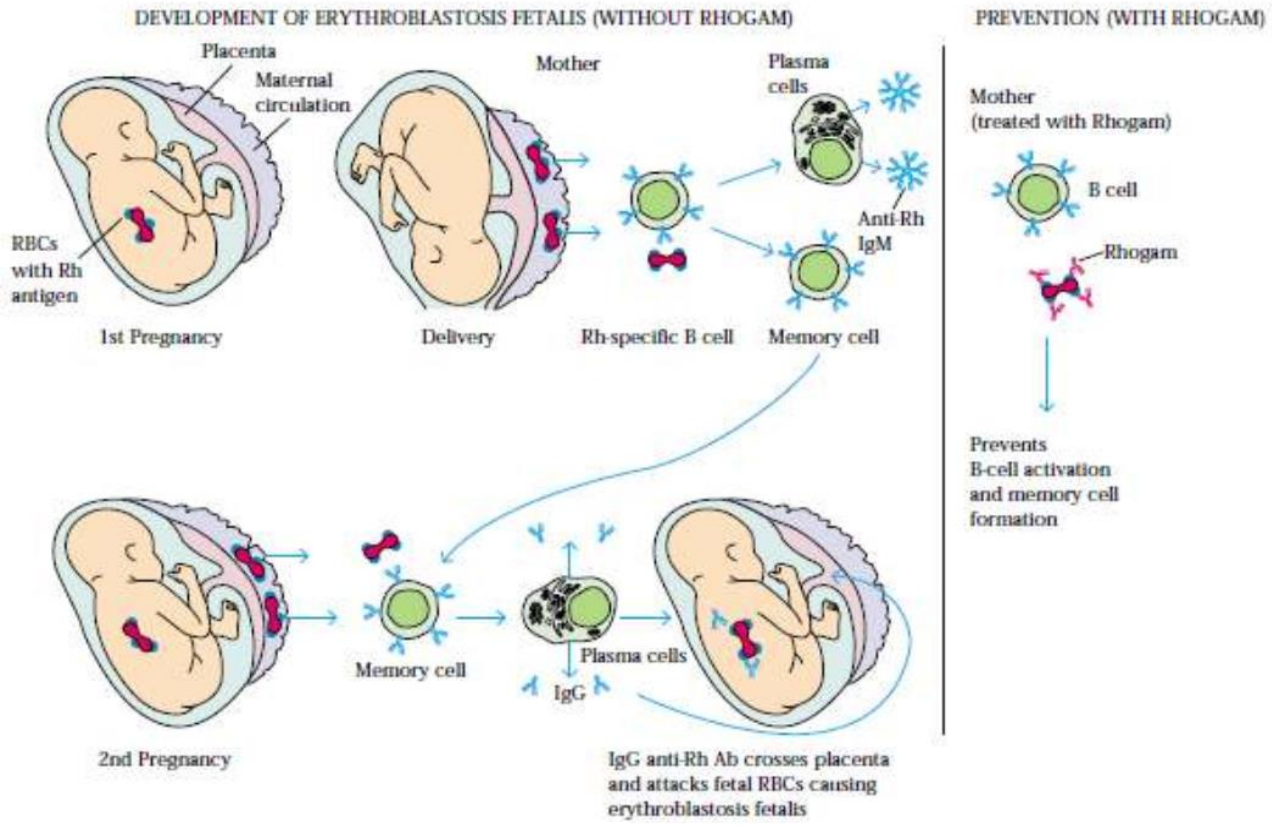
Type II hypersensitive reactions involve antibody-mediated destruction of cells. Antibody can activate the complement system, creating pores in the membrane of a foreign cell (see Figure 13-5), or it can mediate cell destruction by antibody dependent cell-mediated cytotoxicity (ADCC). In this process, cytotoxic cells with Fc receptors bind to the Fc region of antibodies on target cells and promote killing of the cells (see Figure 14-12).Antibody bound to a foreign cell also can serve as an opsonin, enabling phagocytic cells with Fc or C3b receptors to bind and phagocytose the antibody-coated cell.

Hemolytic Disease of the Newborn Is Caused by Type II Reactions

Hemolytic disease of the newborn develops when maternal IgG antibodies specific for fetal blood-group antigens cross the placenta and destroy fetal red blood cells. The consequences of such transfer can be minor, serious, or lethal. Severe hemolytic disease of the newborn, called **erythroblastosis fetalis,** most commonly develops when an Rh^+ fetus expresses an **Rh antigen** on its blood cells that the Rh^- mother does not express.

During pregnancy, fetal red blood cells are separated from the mother's circulation by a layer of cells in the placenta called the trophoblast. During her first pregnancy with an Rh^+ fetus, an Rh^- woman is usually not exposed to enough fetal red blood cells to activate her Rh-specific B cells. At the time of delivery, however, separation of the placenta from the uterine wall allows larger amounts of fetal umbilical-cord blood to enter the mother's circulation. This fetal red blood cells activate Rh-specific B cells, resulting in production of Rh-specific plasma cells and memory B cells in the mother.

The secreted IgM antibody clears the Rh^+ fetal red cells from the mother's circulation, but the memory cells remain a threat to any subsequent pregnancy with an Rh^+ fetus. Activation of these memory cells in a subsequent pregnancy results in the formation of IgG anti-Rh antibodies, which cross the placenta and damage the fetal red blood cells (see Figure). Mild to severe anemia can develop in the fetus, sometimes with fatal consequences. In addition, conversion of hemoglobin to bilirubin can present an additional threat to the newborn because the lipid-soluble bilirubin may accumulate in the brain and cause brain damage. Hemolytic disease of the newborn caused by Rh incompatibility in a subsequent pregnancy can be almost entirely prevented by administering antibodies against the Rh antigen to the mother within 24–48 h after the first delivery.



These antibodies, called **Rhogam,** bind to any fetal red blood cells that enter the mother's circulation at the time of delivery and facilitate their clearance before B-cell activation and ensuing memory-cell production can take place. In a subsequent pregnancy with an Rh^+ fetus, a mother who has been treated with Rhogam is unlikely to produce IgG anti-Rh antibodies; thus, the fetus is protected from the damage that would occur when these antibodies crossed the placenta.

The development of hemolytic disease of the newborn caused by Rh incompatibility can be detected by testing maternal serum at intervals during pregnancy for antibodies to the Rh antigen. A rise in the titer of these antibodies as pregnancy progresses indicates that the mother has been exposed to Rh antigens and is producing increasing amounts of antibody. The presence of maternal IgG on the surface of fetal red blood cells can be detected by a Coombs test. Isolated fetal red blood cells are incubated with the Coombs reagent, goat antibody to human IgG antibody. If maternal IgG is bound to the fetal red blood cells, the cells agglutinate with the Coombs reagent.

If hemolytic disease caused by Rh incompatibility is detected during pregnancy, the treatment depends on the severity of the reaction. For a severe reaction, the fetus can be given an intrauterine blood-exchange transfusion to replace fetal Rh^+ red blood cells with Rh^- cells. These transfusions are given every 10–21 days until delivery. In less severe cases, a blood-exchange

transfusion is not given until after birth, primarily to remove bilirubin; the infant is also exposed to low levels of UV light to break down the bilirubin and prevent cerebral damage. The mother can also be treated during the pregnancy by **plasmapheresis.** In this procedure, a cell separation machine is used to separate the mother's blood into two fractions, cells and plasma. The plasma containing the anti-Rh antibody is discarded, and the cells are reinfused into the mother in an albumin or fresh-plasma solution.

The majorities of cases (65%) of hemolytic disease of the newborn has minor consequences and are caused by ABO blood-group incompatibility between the mother and fetus. Type A or B fetuses carried by type O mothers most commonly develop these reactions. A type O mother is most Likely to develop IgG antibody to the A or B blood-group antigens either through natural exposure or through exposure to fetal blood-group A or B antigens in successive pregnancies.

Usually the fetal anemia resulting from this incompatibility is mild; the major clinical manifestation is a slight elevation of bilirubin, with jaundice. Depending on the severity of the anemia and jaundice, a blood-exchange transfusion may be required in these infants. In general the reaction is mild, however, and exposure of the infant to low levels of UV light is enough to break down the bilirubin and avoid cerebral damage.

Immune Complex–Mediated (Type III) Hypersensitivity

The reaction of antibody with antigen generates immune complexes. Generally this complexing of antigen with antibody facilitates the clearance of antigen by phagocytic cells. In some cases, however, large amounts of immune complexes can lead to tissue-damaging type III hypersensitive reactions. The magnitude of the reaction depends on the quantity of immune complexes as well as their distribution within the body.

When the complexes are deposited in tissue very near the site of antigen entry, a localized reaction develops. When the complexes are formed in the blood, a reaction can develop wherever the complexes are deposited. In particular, complex deposition is frequently observed on blood-vessel walls, in the synovial membrane of joints, on the glomerular basement membrane of the kidney, and on the choroid plexus of the brain. The deposition of these complexes initiates a reaction that results in the recruitment of neutrophils to the site. The tissue there is injured as a consequence of granular release from the neutrophil.

Type III hypersensitive reactions develop when immune complexes activate the complement system's array of immune effector molecules. As explained previously, the C3a, C4a, and C5a complement split products are anaphylatoxins that cause localized mast-cell degranulation and consequent increase in local vascular permeability. C3a, C5a, and C5b67 are also chemotactic factors for neutrophils, which can accumulate in large numbers at the site of immune-complex deposition.

Larger immune complexes are deposited on the basement membrane of blood vessel walls or kidney glomeruli, whereas smaller complexes may pass through the basement membrane and be deposited in the subepithelium. The type of lesion that results depends on the site of deposition of the complexes. Much of the tissue damage in type III reactions stems from release of lytic enzymes by neutrophils as they attempt to phagocytose immune complexes. The C3b complement component acts as an opsonin, coating immune complexes.

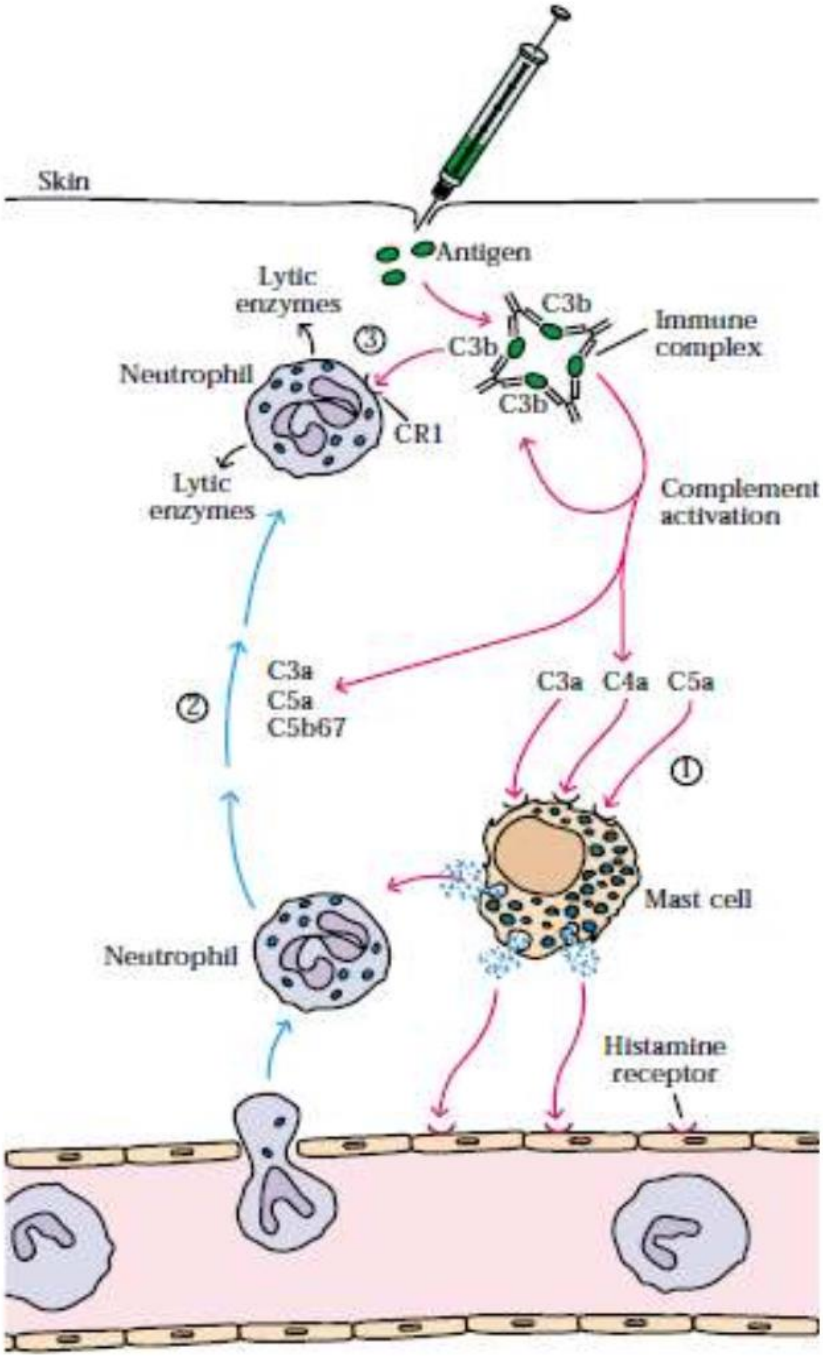
A neutrophil binds to a C3b-coated immune complex by means of the type I complement receptor, which is specific for C3b. Because the complex is deposited on the basement membrane surface, phagocytosis is impeded, so that lytic enzymes are released during the unsuccessful attempts of the neutrophil to ingest the adhering immune complex. Further activation of the membrane-attack mechanism of the complement system can also contribute to the destruction of tissue. In addition, the activation of complement can induce aggregation of platelets, and the resulting release of clotting factors can lead to formation of microthrombi.

Type III Reactions Can Be Localized

Injection of an antigen intradermally or subcutaneously into an animal that has high levels of circulating antibody specific for that antigen leads to formation of localized immune complexes, which mediate an acute Arthus reaction within 4–8 h (see Figure).Microscopic examination of the tissue reveals neutrophils adhering to the vascular endothelium and then migrating into the tissues at the site of immune complex deposition. As the reaction develops, localized tissue and vascular damage results in an accumulation of fluid (edema) and red blood cells (erythema) at the site. The severity of the reaction can vary from mild swelling and redness to tissue necrosis.

After an insect bite, a sensitive individual may have a rapid, localized type I reaction at the site. Often, some 4–8 h later, a typical Arthus reaction also develops at the site, with pronounced erythema and edema. Intrapulmonary Arthus-type reactions induced by bacterial spores, fungi, or dried fecal proteins can also cause pneumonitis or alveolitis. These reactions are known by a variety

of common names reflecting the source of the antigen. For example, “farmer’s lung” develops after inhalation of thermophilic actinomycetes from moldy hay, and “pigeon fancier’s disease” results from inhalation of a serum protein in dust derived from dried pigeon feces.



Development of a localized Arthus reaction (type III hypersensitive reaction). Complement activation initiated by immune complexes (classical pathway) produces complement intermediates that (1) mediate mast-cell degranulation, (2) chemotactically attract neutrophils, and (3) stimulate release of lytic enzymes from neutrophils trying to phagocytose C3b-coated immune complexes.

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Hypersensitivity (DTH)

When some subpopulations of activated T_H cells encounter certain types of antigens, they secrete cytokines that induce a localized inflammatory reaction called delayed-type hypersensitivity (DTH). The reaction is characterized by large influxes of nonspecific inflammatory cells, in particular, macrophages. This type of reaction was first described in 1890 by Robert Koch, who observed that individuals infected with *Mycobacterium tuberculosis* developed a localized inflammatory response when injected intradermally with a filtrate derived from a mycobacterial culture. He called this localized skin reaction a "tuberculin reaction."

Later, as it became apparent that a variety of other antigens could induce this response (see Table), its name was changed to delayed-type or type IV hypersensitivity in reference to the delayed onset of the reaction and to the tissue damage (hypersensitivity) that is often associated with it.

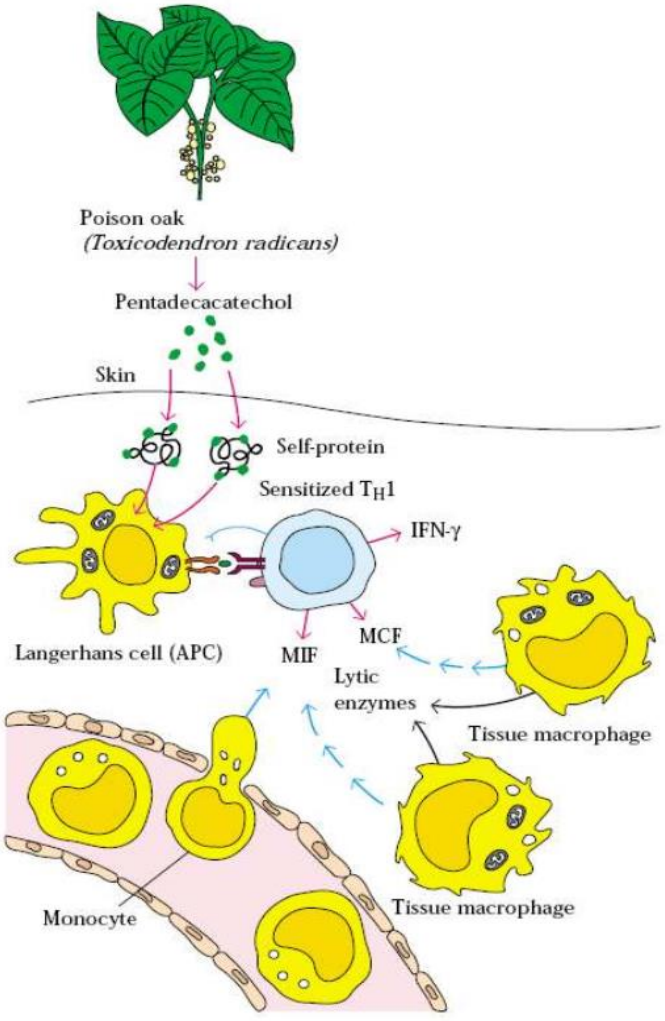
Intracellular bacteria	Intracellular viruses
Mycobacterium tuberculosis	Herpes simplex virus
Mycobacterium leprae	Variola (smallpox)
Listeria monocytogenes	Measles virus
Brucella abortus	
Intracellular fungi	Contact antigens
Pneumocystis carinii	Picrylchloride
Candida albicans	Hair dyes
Histoplasma capsulatum	Nickel salts
Cryptococcus neoformans	Poison ivy
	Poison oak
Intracellular parasites	
Leishmania sp.	

Intracellular pathogens and contact antigens that induce delayed type hypersensitive reaction

The term *hypersensitivity* is somewhat misleading, for it suggests that a DTH response is always detrimental. Although in some cases a DTH response does cause extensive tissue damage and is in itself pathologic, in many cases tissue damage is limited, and the response plays an important role in defense against intracellular pathogens and contact antigens. The hallmarks of a type IV reaction are the delay in time required for the reaction to develop and the recruitment of macrophages as opposed to neutrophils, as found in a type III reaction. Macrophages are the major component of the infiltrate that surrounds the site of inflammation.

Contact Dermatitis Is a Type of DTH Response

Many contact-dermatitis reactions, including the responses to formaldehyde, trinitrophenol, nickel, turpentine, and active agents in various cosmetics and hair dyes, poison oak, and poison ivy, are mediated by T_H1 cells. Most of these substances are small molecules that can complex with skin proteins. This complex is internalized by antigen-presenting cells in the skin (e.g., Langerhans cells), then processed and presented together with class II MHC molecules, causing activation of sensitized T_H1 cells. In the reaction to poison oak, for example, a pentadecacatechol compound from the leaves of the plant forms a complex with skin proteins. When T_H cells react with this compound appropriately displayed by local antigen-presenting cells, they differentiate into sensitized T_H1 cells. A subsequent exposure to pentadecacatechol will elicit activation of T_H1 cells and induce cytokine production (see Figure).



Approximately 48–72 h after the second exposure, the secreted cytokines cause macrophages to accumulate at the site. Activation of these macrophages and release of lytic enzymes result in the redness and pustules that characterize a reaction to poison oak.

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Autoimmunity

Early in the last century, paul ehrlich, realized that the immune system could go awry and, instead of reacting against foreign antigens, could focus its attack on self-antigens. He termed this condition "horror autotoxicus."We now understand that, while mechanisms of self-tolerance normally protect an individual from potentially self-reactive lymphocytes, there are failures. They result in an inappropriate response of the immune system against self-components termed **autoimmunity.**

Common human autoimmune diseases

These can be divided into two broad categories: organ-specific and systemic autoimmune disease (see Table). Such diseases affect 5%–7% of the human population, often causing chronic debilitating illnesses.

Disease	Self-antigen	Immune response
	ORGAN-SPECIFIC AUTOIMMUNE DISEASES	
Addison's disease	Adrenal cells	Auto-antibodies
Autoimmune hemolytic anemia	RBC membrane proteins	Auto-antibodies
Goodpasture's syndrome	Renal and lung basement membranes	Auto-antibodies
Graves' disease	Thyroid-stimulating hormone receptor	Auto-antibody (stimulating)
Hashimoto's thyroiditis	Thyroid proteins and cells	T_{DTH} cells, auto-antibodies
Idiopathic thrombocyopenia purpura	Platelet membrane proteins	Auto-antibodies
Insulin-dependent diabetes mellitus	Pancreatic beta cells	T_{DTH} cells, auto-antibodies
Myasthenia gravis	Acetylcholine receptors	Auto-antibody (blocking)
Myocardial infarction	Heart	Auto-antibodies
Pernicious anemia	Gastric parietal cells; intrinsic factor	Auto-antibody
Poststreptococcal glomerulonephritis	Kidney	Antigen-antibody complexes
Spontaneous infertility	Sperm	Auto-antibodies
	SYSTEMIC AUTOIMMUNE DISEASES	
Ankylosing sponkylitis	Vertebrae	Immune complexes
Multiple sclerosis	Brain or white matter	T_H1 cells and T_C cells, auto-antibodies
Rheumatoid arthritis	Connective tissue, IgG	Auto-antibodies, immune complexes
Scleroderma	Nuclei, heart, lungs, gastrointestinal tract, kidney	Auto-antibodies
Sjogren's syndrome	Salivary gland, liver, kidney, thyroid	Auto-antibodies
Systemic lupus erythematosus (SLE)	DNA, nuclear protein, RBC and platelet membranes	Auto-antibodies, immune complexes

Organ-Specific Autoimmune Diseases

In an organ-specific autoimmune disease, the immune response is directed to a target antigen unique to a single organ or gland, so that the manifestations are largely limited to that organ. The cells of the target organs may be damaged directly by humoral or cell-mediated effector

mechanism. Alternatively, the antibodies may overstimulate or block the normal function of the target organ.

Some Autoimmune Diseases Are Mediated by Direct Cellular Damage

Autoimmune diseases involving direct cellular damage occur when lymphocytes or antibodies bind to cell-membrane antigens, causing cellular lysis and/or an inflammatory response in the affected organ. Gradually, the damaged cellular structure is replaced by connective tissue (scar tissue), and the function of the organ declines. This section briefly describes a few examples of this type of autoimmune disease.

Hashimoto's Thyroiditis

In Hashimoto's thyroiditis, which is most frequently seen in middle-aged women, an individual produces auto-antibodies and sensitized T_H1 cells specific for thyroid antigens. The DTH response is characterized by an intense infiltration of the thyroid gland by lymphocytes, macrophages, and plasma cells, which form lymphocytic follicles and germinal centers. The ensuing inflammatory response causes a goiter, or visible enlargement of the thyroid gland, a physiological response to hypothyroidism. Antibodies are formed to a number of thyroid proteins, including thyroglobulin and thyroid peroxidase, both of which are involved in the uptake of iodine. Binding of the auto-antibodies to these proteins interferes with iodine uptake and leads to decreased production of thyroid hormones (hypothyroidism).

Goodpasture's Syndrome

In **Goodpasture's syndrome,** auto-antibodies specific for certain basement-membrane antigens bind to the basement membranes of the kidney glomeruli and the alveoli of the lungs. Subsequent complement activation leads to direct cellular damage and an ensuing inflammatory response mediated by a buildup of complement split products. Damage to the glomerular and alveolar basement membranes lead to progressive kidney damage and pulmonary hemorrhage. Death may ensue within several months of the onset of symptoms. Biopsies from patients with Goodpasture's syndrome stained with fluorescent-labeled anti-IgG and anti- C3b reveal linear deposits of IgG and C3b along the basement membranes.

Some Autoimmune Diseases Are Mediated by Stimulating or Blocking Auto-Antibodies

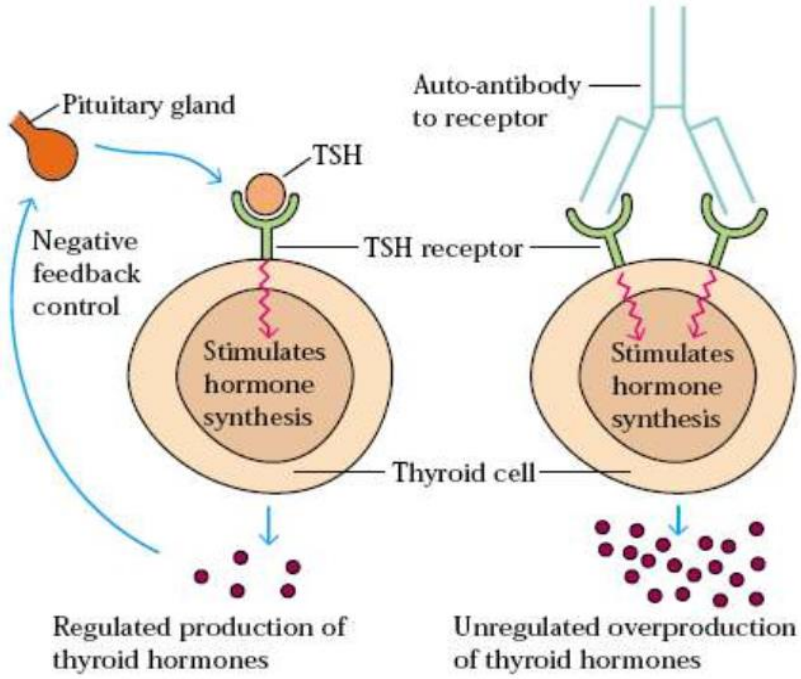
In some autoimmune diseases, antibodies act as agonists, binding to hormone receptors in lieu of the normal ligand and stimulating inappropriate activity. This usually leads to an overproduction of mediators or an increase in cell growth. Conversely, auto-antibodies may act as

antagonists, binding hormone receptors but blocking receptor function. This generally causes impaired secretion of mediators and gradual atrophy of the affected organ.

Graves' disease

The production of thyroid hormones is carefully regulated by thyroid-stimulating hormone (TSH), which is produced by the pituitary gland. Binding of TSH to a receptor on thyroid cells activates adenylate cyclase and stimulates the synthesis of two thyroid hormones, thyroxine and triiodothyronine. A patient with **Graves' disease** produces auto-antibodies that bind the receptor for TSH and mimic the normal action of TSH, activating adenylate cyclase and resulting in production of the thyroid hormones. Unlike TSH, however, the autoantibodies are not regulated, and consequently they overstimulate the thyroid. For this reason these auto-antibodies are called long-acting thyroid-stimulating (LATS) antibodies (see Figure).

STIMULATING AUTO-ANTIBODIES (Graves' disease)



Myasthenia Gravis

Myasthenia gravis is the prototype autoimmune disease mediated by blocking antibodies. A patient with this disease produces auto-antibodies that bind the acetylcholine receptors on the motor end-plates of muscles, blocking the normal binding of acetylcholine and also inducing complement mediated lysis of the cells. The result is a progressive weakening of the skeletal muscles (see Figure).

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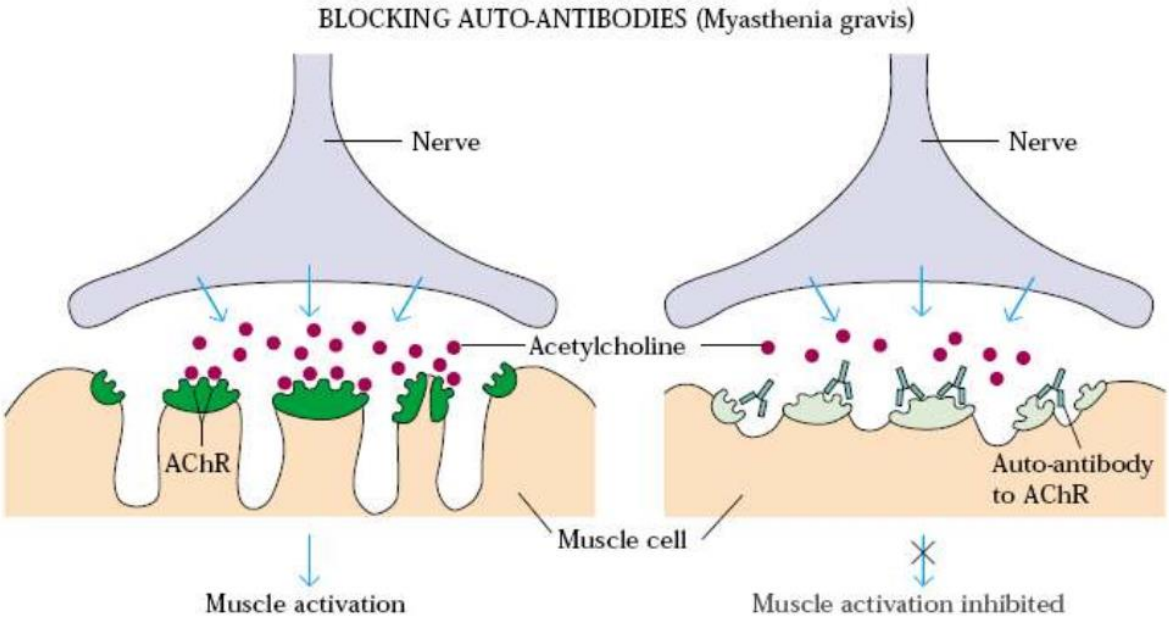

Ultimately, the antibodies destroy the cells bearing the receptors. The early signs of this disease include drooping eyelids and inability to retract the corners of the mouth, which gives the appearance of snarling. Without treatment, progressive weakening of the muscles can lead to severe impairment of eating as well as problems with movement. However, with appropriate treatment, this disease can be managed quite well and afflicted individuals can lead a normal life.