Hypersensivity disorders

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Causes of Hypersensitivity Diseases

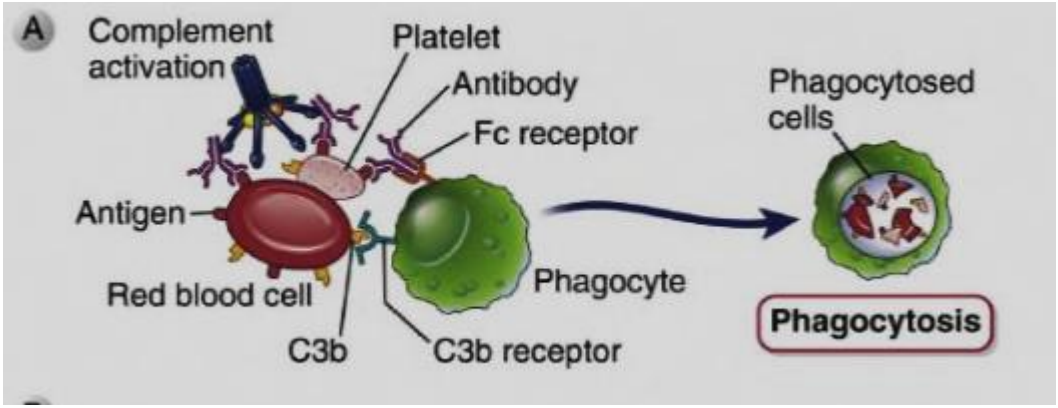
- **Reactions against self antigens: autoimmunity**.
- Failure of the normal mechanisms of self-tolerance results in T cell and B cell reactions against one's own cells and tissues.
- **Reactions against microbes**. Immune responses against microbial antigens may cause disease if the reactions are excessive or the microbes are unusually resistant to eradication and thus the infections are persistent.
- If antibodies are produced against microbial antigens, the antibodies may bind to the antigens to produce immune complexes, which deposit in tissues and trigger inflammation.
- **Reactions against nonmicrobial environmental antigens**. Most healthy individuals do not react against common, generally harmless environmental substances, but 20% or more of the population is abnormally responsive to one or more of these substances.
- These individuals produce IgE (immunoglobulin E) antibodies that cause allergic diseases.

Mechanisms and Classification of Hypersensitivity Reactions

Hypersensitivity diseases are commonly classified according to the type of immune response and the effector mechanism responsible for cell and tissue injury

- **Immediate** (type I hypersensitivity is caused by IgE antibodies specific for nonmicobial environmental antigens and is the most prevalent type of hypersensitivity disease.
- Immediate hypersensitivity diseases, commonly grouped under allergy or atopy, are often caused by activation of interleukin-4 (IL-4), IL-5, and IL-13 producing Th2 cells and the production of IgE antibodies, which activate mast cells and eosinophils and induce inflammation.
- **Antibody-mediated** (type II) hypersensitivity. IgG and IgM antibodies specific for cell surface or extracellular matrix antigens can cause tissue injury by activating the complement system, targeting cells for phagocytosis by leukocytes, recruiting inflammatory cells, and interfering with normal cellular functions.
- **Immune complex-mediated** (type III) hypersensitivity. IgM and IgG antibodies specific for soluble antigens in the blood form complexes with the antigens, and the immune complexes may deposit in blood vessel walls in various tissues, causing inflammation, thrombosis, and tissue injury.
- **T cell-mediated** (type IV) hypersensitivity. In these disorders, tissue injury may be due to CD4+ T lymphocytes, which secrete cytokines that induce inflammation, or CD8+ CTLs, which kill target cells.

Diseases Caused by Antibodies and Antigen Antibody Complexes



- Antibody-mediated diseases are caused either by antibodies that bind to antigens on particular cells or in extracellular tissues or by antigenantibody complexes that form in the circulation and are deposited in vessel walls.

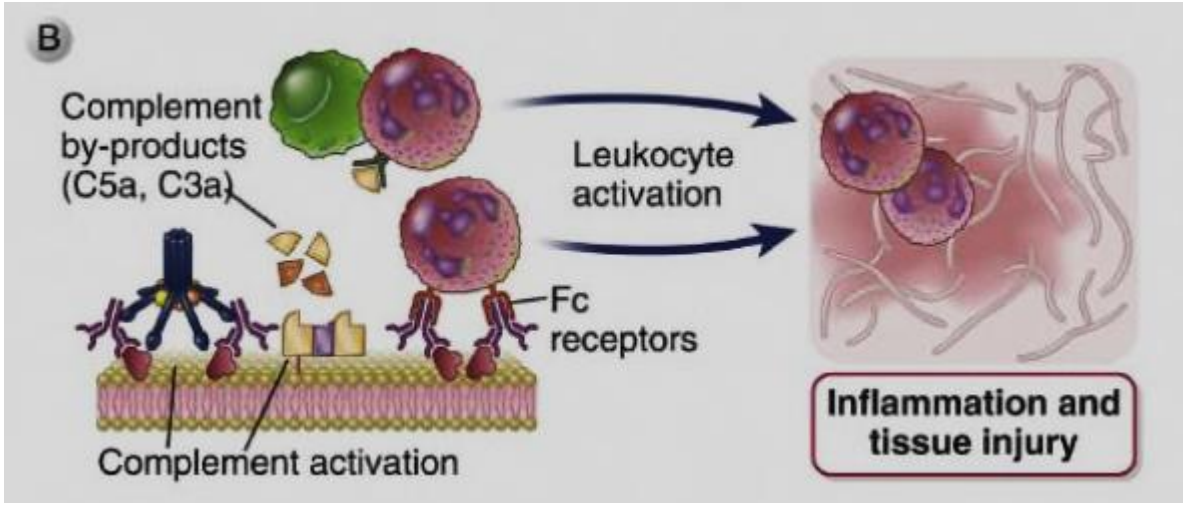
Diseases Caused by Antibodies Against Fixed Cell and Tissue Antigens

- Antibody-mediated diseases are produced by antibodies that bind to antigens on particular cells or in extracellular tissues.

Opsonization and phagocytosis. Antibodies that bind to surface antigens on circulating cells may opsonize these cells, or they may activate the complement system, resulting in the production of complement proteins that opsonize the cells.

- These opsonized cells are phagocytosed and destroyed by phagocytes that express receptors for the Fc portions of IgG antibodies and receptors for complement proteins.
- This is the principal mechanism of cell destruction in autoimmune hemolytic anemia and autoimmune thrombocytopenia, in which antibodies specific for red blood cells or platelets, respectively, lead to the opsonization and removal of these cells from the circulation.
- Antibody coated red cells and platelets may also be lysed by the membrane attack complex of complement.
- The same mechanisms are responsible for hemolysis in transfusion reactions.

Diseases Caused by Antibodies and Antigen Antibody Complexes

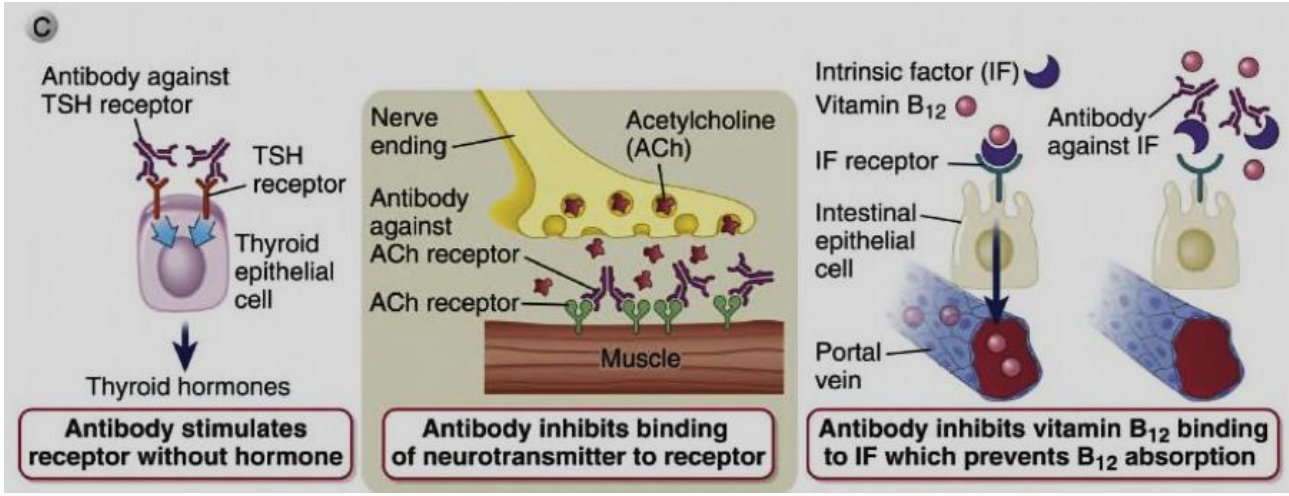


Diseases Caused by Antibodies Against Fixed Cell and Tissue Antigens

Inflammation. Antibodies deposited in tissues activate complement, leading to the liberation of breakdown products such as C5a and C3a, which recruit neutrophils and macrophages.

- These leukocytes express IgG Fc receptors and complement receptors, which bind the antibodies or attached complement proteins.
- The leukocytes are activated by signaling from the receptors (particularly Fc receptors), and leukocyte products (including lysosomal enzymes and reactive oxygen species) are released and cause tissue injury. Free antibodies most often deposit in basement membranes and extracellular matrix.
- An example of antibody-mediated inflammation and leukocyte activation causing tissue injury is glomerulonephritis caused by antibodies against the glomerular basement membrane (called Goodpasture syndrome if the antibodies also bind to basement membranes in the lungs).

Diseases Caused by Antibodies and Antigen Antibody Complexes

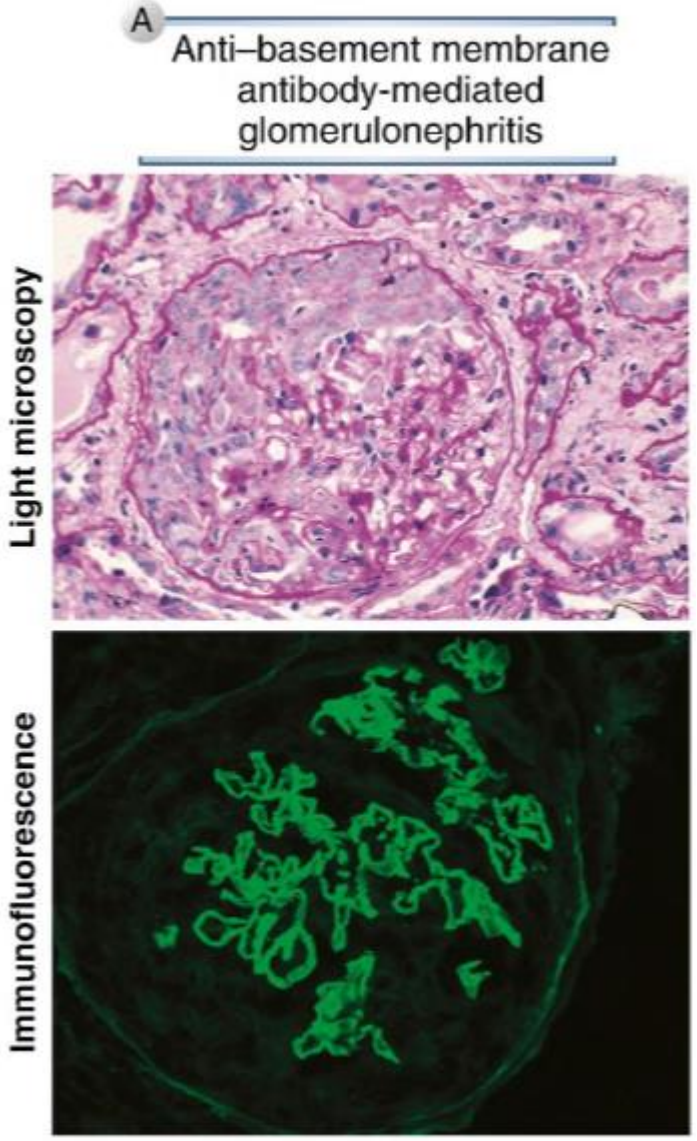


Diseases Caused by Antibodies Against Fixed Cell and Tissue Antigens

Abnormal cellular functions. Antibodies that bind to normal cellular receptors or other proteins may interfere with the functions of these receptors or proteins and cause disease without inflammation or tissue damage.

- For instance, antibodies specific for the thyroid-stimulating hormone receptor or the nicotinic acetylcholine receptor cause functional abnormalities that lead to Graves' disease and myasthenia gravis, respectively.
- Antibodies specific for intrinsic factor, required for vitamin B2 absorption, cause pernicious anemia. Antibodies specific for cytokines are rare but known causes of immunodeficiencies.

Diseases Caused by Antibodies and Antigen Antibody Complexes

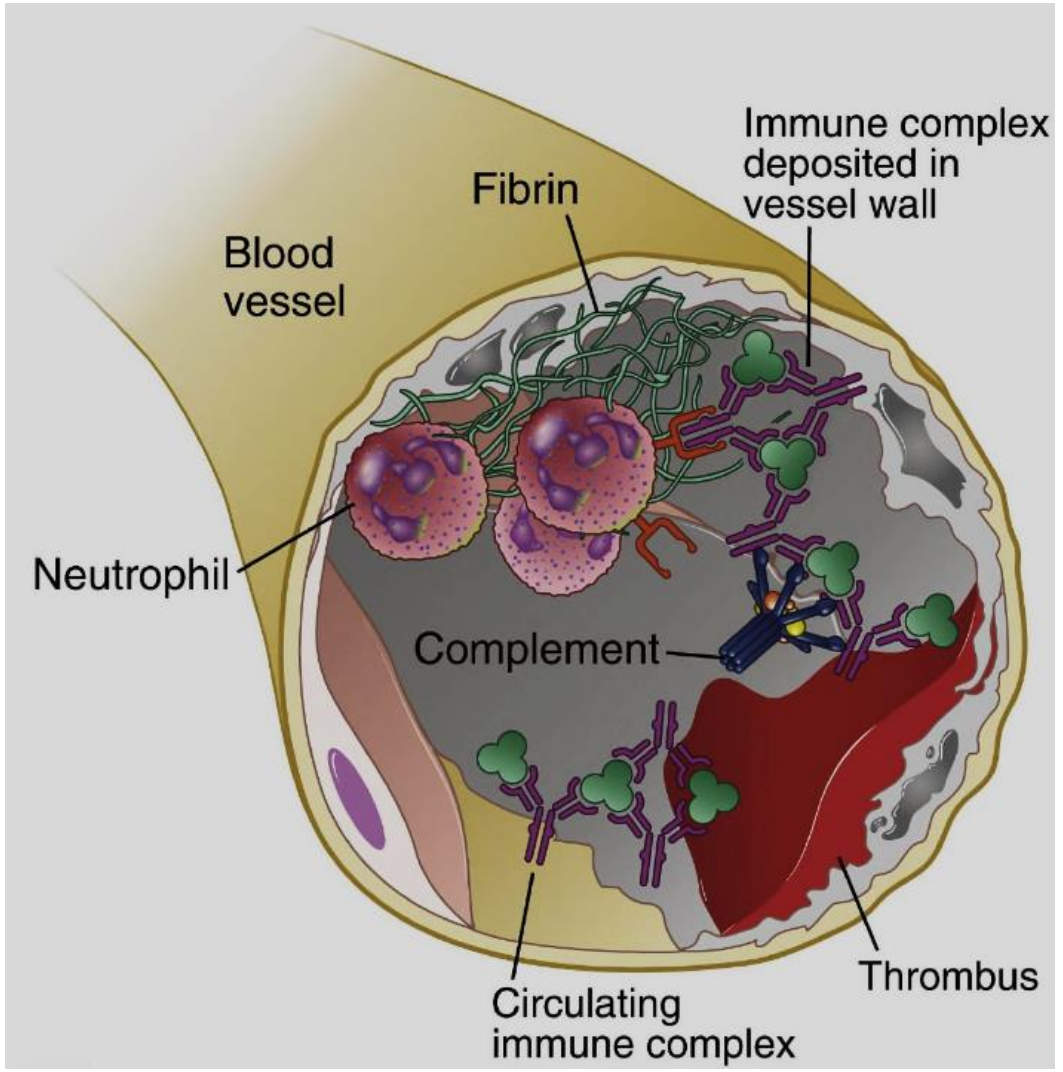


Diseases Caused by Antibodies Against Fixed Cell and Tissue Antigens

Antibodies that cause cell- or tissue-specific diseases are usually autoantibodies produced as part of an autoimmune reaction, but sometimes the antibodies are specific for microbes.

- Less commonly, the antibodies may be produced against a foreign (e.g., microbial) antigen that is immunologically cross-reactive with a component of self tissues.
- In a rare sequel to streptococcal infection called rheumatic fever, antibodies produced against the bacteria cross-react with antigens in the heart, deposit in this organ, and cause inflammation and tissue damage.
- Tissue deposits of antibodies may be detected by pathologic examination in some of these diseases, and the deposition of antibody is often associated with local complement activation, inflammation, and tissue injury.

Diseases Caused by Antibodies and Antigen Antibody Complexes

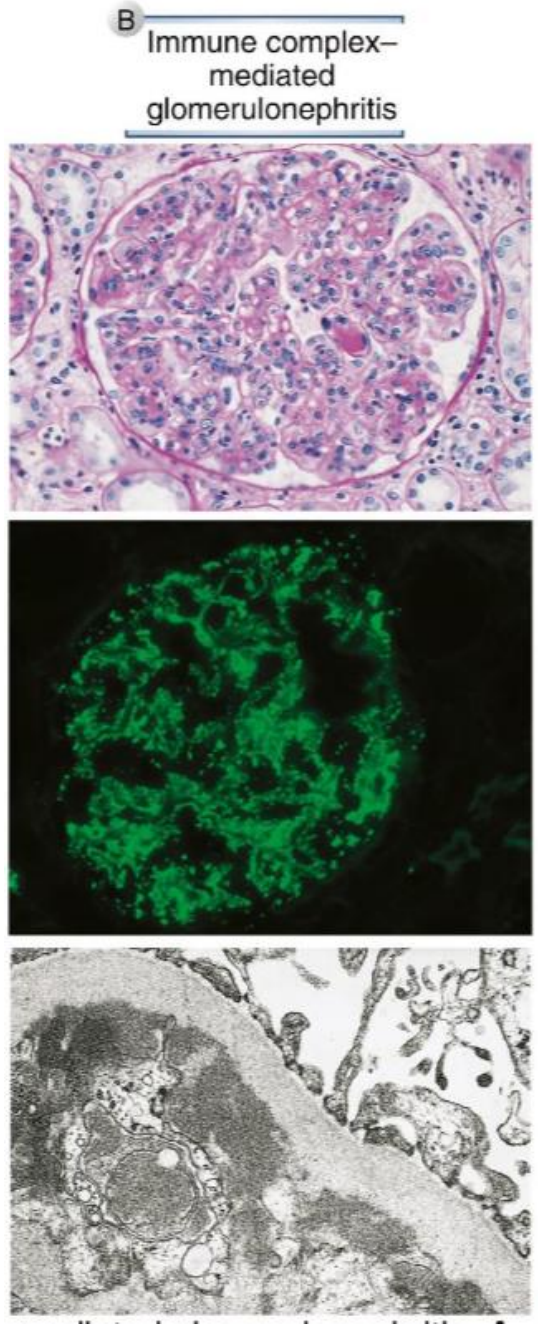


Diseases Caused by Antibodies Against Fixed Cell and Tissue Antigens

Immune complex-mediated diseases are usually caused by antigenantibody complexes that form in the circulation and are deposited in multiple tissues, producing systemic disorders.

- The immune complexes that cause disease may be composed of antibodies bound to either self antigens or foreign antigens.
- Almost all of these diseases are systemic, but a few are restricted to kidneys, perhaps because, in those cases, complexes are formed only in the glomerular basement membrane.

Diseases Caused by Antibodies and Antigen Antibody Complexes



Diseases Caused by Antibodies Against Fixed Cell and Tissue Antigens

Pathogenesis of Immune Complex—Mediated Diseases

Glomerulonephritis induced by the deposition of immune complexes (systemic lupus erythematosus).

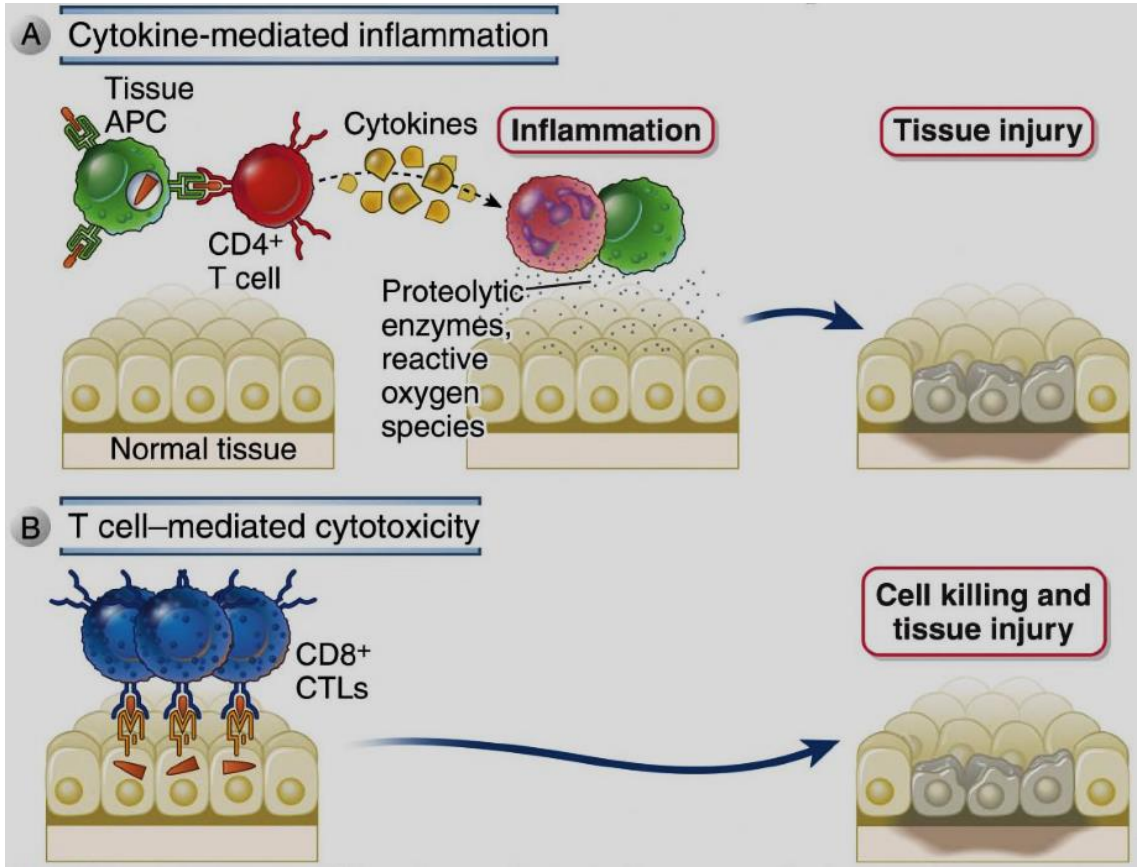
- The amount of immune complex deposition in tissues is determined by the nature of the complexes and the characteristics of the blood vessels.
- The major mechanism of tissue injury in immune complex diseases is inflammation within the walls of blood vessels that occurs when the antibodies of deposited complexes activate complement and bind to leukocyte Fc receptors.
- Many systemic immunologic diseases in humans are caused by the deposition of immune complexes in blood vessels (Systemic lupus erythematosus (SLE), polyarteritis nodosa, poststreptococcal glomerulonephritis, Serum Sickness).

Diseases Caused by T Lymphocytes

- T lymphocytes injure tissues by either producing cytokines that induce inflammation or directly killing target cells.

Diseases Caused by Cytokine-Mediated Inflammation

- In immune-mediated inflammation, Th1 and Th17 cells secrete cytokines that recruit and activate leukocytes.
- Many organ-specific autoimmune diseases are caused by activation of autoreactive T cells by self antigens, leading to cytokine release and inflammation.
- T cell responses specific for microbes and other foreign antigens may also lead to inflammation and tissue injury.
- A variety of skin diseases, called contact sensitivity, result from topical exposure to chemicals and environmental antigens.

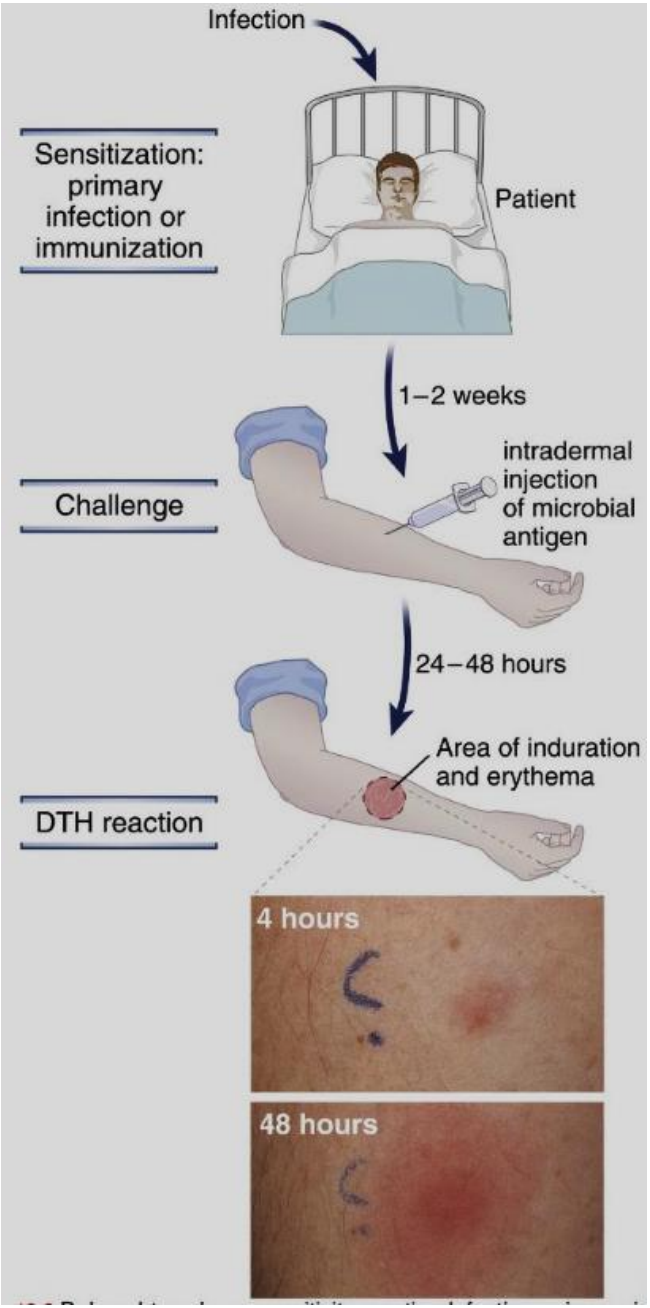


Diseases Caused by T Lymphocytes

Diseases Caused by Cytokine-Mediated Inflammation

Delayed-Type Hypersensitivity (DTH)

- DTH is an injurious cytokine-mediated inflammatory reaction resulting from the activation of T cells, particularly CD4 + T cells.
- The reaction is called delayed because it typically develops 24 to 48 hours after antigen challenge in a previously immunized (sensitized) individual, in contrast to immediate hypersensitivity (allergic) reactions, which develop within minutes.
- In clinical practice, loss of DTH responses to universally encountered antigens (e.g., Candida antigens) is an indication of deficient T cell function, a condition known as anergy.
- Although DTH has traditionally been considered a Th1-mediated injurious reaction, other T cells may contribute to the inflammation.
- Chronic DTH reactions and fibrosis can develop if a Th1 response to an infection activates macrophages but fails to eliminate phagocytosed microbes.

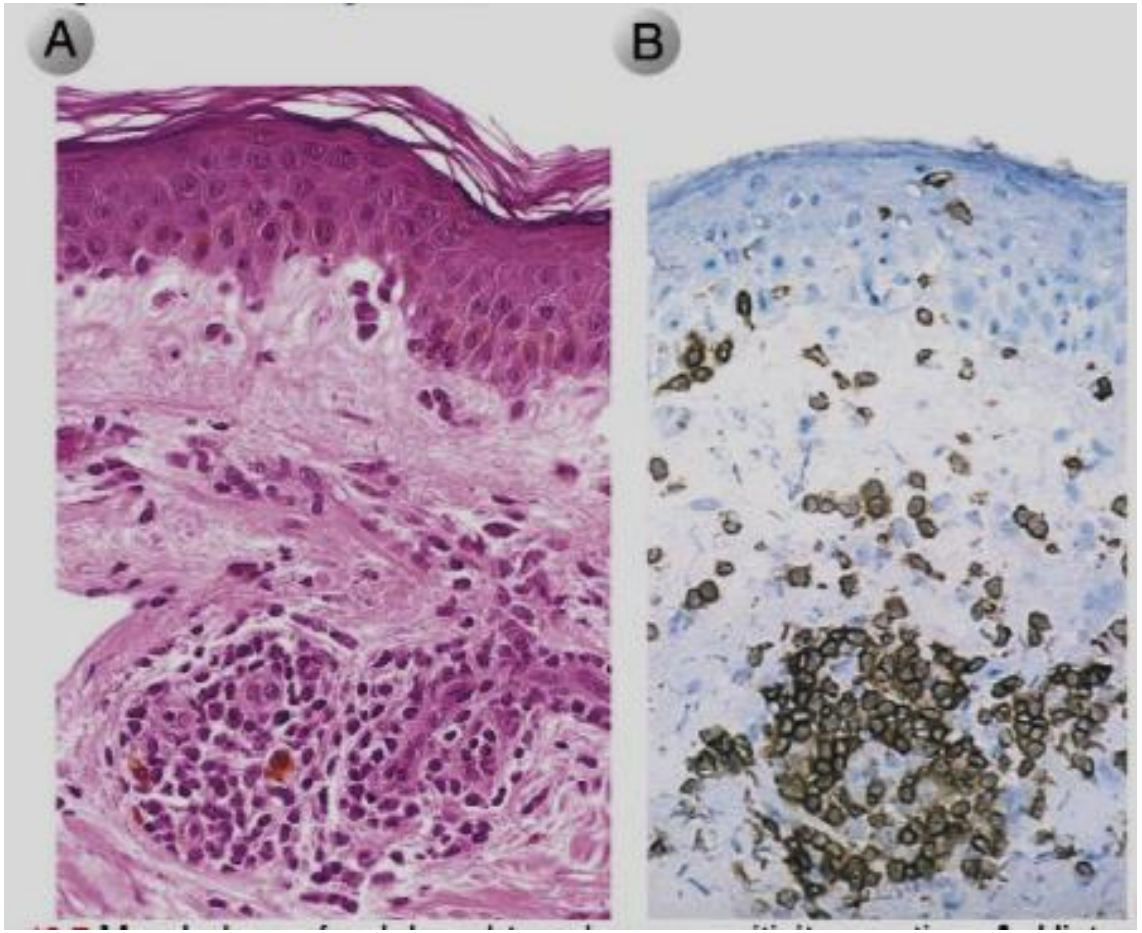


Diseases Caused by T Lymphocytes

Diseases Caused by Cytokine-Mediated Inflammation

Delayed-Type Hypersensitivity (DTH)

- Morphology of a delayed-type hypersensitivity reaction:
- A, Histopathologic examination of the reaction in skin shows perivascular mononuclear cell infiltrates in the dermis.
- At higher magnification, the infiltrate is seen to consist of activated lymphocytes and macrophages surrounding small blood vessels in which the endothelial cells are also activated.
- B, Immunohistochemical staining demonstrates the presence of many CD4+ T lymphocytes.

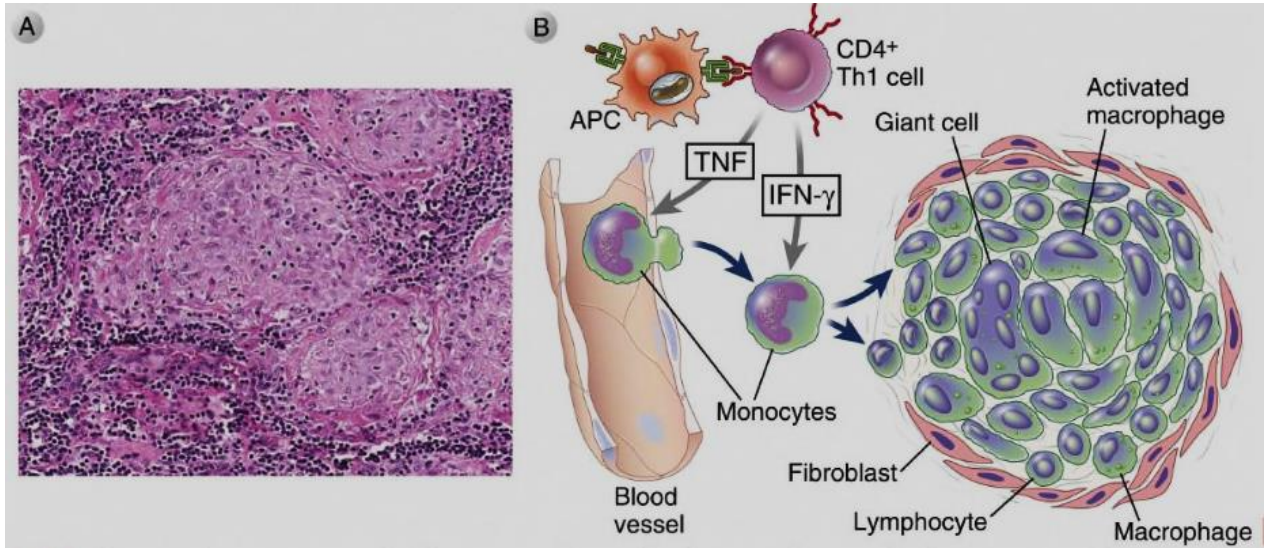


Diseases Caused by T Lymphocytes

Diseases Caused by Cytokine-Mediated Inflammation

Granulomatous inflammation

- A, Lymph node from a patient with tuberculosis containing granulomas with activated macrophages, multinucleate giant cells, and lymphocytes.
- In some granulomas, there may be a central area of necrosis.
- Immunohistochemical studies would identify the lymphocytes as T cells.
- B, Mechanisms of granuloma formation.
- Cytokines are involved in the generation of Th1 cells, activation of macrophages, and recruitment of leukocytes.
- Prolonged reactions of this type lead to the formation of granulomas.



Diseases Caused by T Lymphocytes

Diseases Caused by Cytotoxic T Lymphocytes

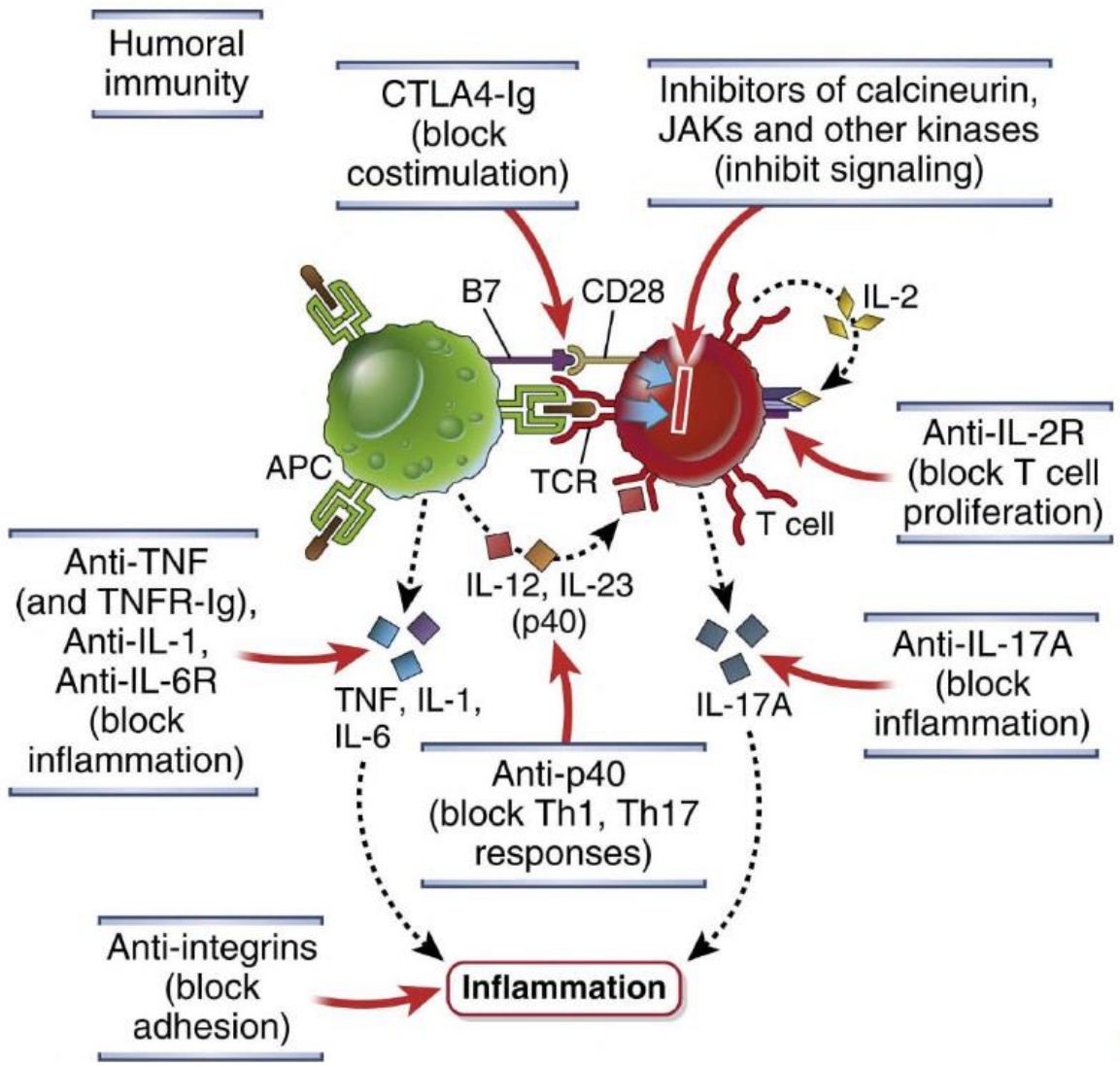
- CTL responses to viral infection can lead to tissue injury by killing infected cells, even if the virus itself has little cytopathic effect.
- The principal physiologic function of CTLs is to eliminate intracellular microbes, primarily viruses, by killing infected cells.
- Some viruses directly injure infected cells and are said to be cytopathic, whereas others are not.
- Because CTLs cannot distinguish between cytopathic and noncytopathic viruses, they kill virus-infected cells regardless of whether the infection itself is harmful to the host.
- Examples of viral infections in which the lesions are mainly due to the host CTL response and not the virus itself include lymphocytic choriomeningitis in mice and certain forms of viral hepatitis in humans.
- CTLs may contribute to tissue injury in autoimmune disorders in which destruction of particular host cells is a prominent component, such as type 1 diabetes, in which insulin-producing B cells in pancreatic islets are destroyed.
- CTLs also cause injury to organ allografts during rejection responses.

Therapeutic Approaches for Immunologic Diseases

- One of the most impressive accomplishments of immunology has been the development of novel therapies for immunologic diseases based on the understanding of fundamental mechanisms of these disorders.

Biologic therapies for inflammatory diseases targeting T cell responses and inflammation.

- Illustrated are the sites of action of some therapeutic agents that block different components of immune and inflammatory responses.
- Many of these agents target cytokines and their receptors.
- B cell depletion by anti-CD20 may also reduce pathologic T cell responses.



Therapeutic Approaches for Immunologic Diseases

Cytokine Antagonists

- The first clinically successful cytokine antagonists targeted TNF and included a soluble form of the TNF receptor and anti-TNF antibodies, which bind to and neutralize TNF.
- These agents are of great benefit in many patients with rheumatoid (RA), Crohn's disease, and psoriasis.
- Antibodies to the IL-6 receptor also have been successfully used in some forms of arthritis.
- Antagonists of other proinflammatory cytokines and their receptors, including IL-1, IL-12, IL-17, and the receptors for IL-12, IL-17, and IL-23, are now approved for various inflammatory diseases, and many others are in clinical trials.
- Antibodies against Th2 cytokines or their receptors are approved for treating allergic diseases.
- In addition to these biologic agents, small molecule inhibitors of Janus kinases (JAKs) (important intracellular signaling mediators of a variety of cytokine receptors) are also approved to inhibit cytokine actions in RA, and inhibitors of other kinases (such as the B cell signaling molecule BTK) are approved for are approved for antibody-mediated disease (e.g., RA and SLE).

Therapeutic Approaches for Immunologic Diseases

Depletion of Cells and Antibodies

- Monoclonal antibodies that deplete all lymphoid cells, only B cells, or only T cells are used to treat inflammatory diseases.
- A recent development is the successful use of anti-CD20 antibody (rituximab), which depletes only B cells, to treat diseases that were thought to be caused primarily by T cell-mediated inflammation.
- This treatment has shown efficacy in patients with RA and MS.
- The effectiveness of anti-CD20 may be related to a role of B cells as antigen presenting cells (APCs) for T cell responses, especially for the generation and maintenance of memory T cells.
- Plasmapheresis has been used to eliminate circulating autoantibodies and immune complexes.

Therapeutic Approaches for Immunologic Diseases

Intravenous IgG

- Intravenous Ig (IVIG) is pooled IgG from healthy donors administered intravenously.
- It has beneficial effects in some autoimmune diseases, such as autoimmune thrombocytopenia and hemolytic anemia.
- It is not clear how this agent, which contains IgG of many unknown specificities, inhibits hypersensitivity reactions.
- One possibility is that the IgG binds to the inhibitory Fc receptor (FcyRIIB) on B lymphocytes and DCs and thus attenuates autoantibody production and inflammatory responses.
- IVIG may also compete with pathogenic antibodies for binding to the neonatal Fe receptor (FcRn), which functions in adults to protect antibodies from catabolism, resulting in reduced half-lives of the pathogenic antibodies.

Therapeutic Approaches for Immunologic Diseases

Tolerance-Inducing Therapies

- There are ongoing attempts at more specific treatments for adaptive immune mediated inflammatory diseases, such as inducing tolerance in disease-producing T cells.
- MS and type 1 diabetes are two diseases in which the target antigens have been defined; in both disorders, clinical trials are underway in which the antigens (peptides of myelin basic protein [MBP] and insulin, respectively) are administered to patients in ways that inhibit lymphocytes specific for the antigens.
- A risk with many treatments that block various components of the immune system is that these will interfere with the normal function of the immune system in combating microbes and thus make individuals susceptible to infections.
- Antigen-specific tolerance avoids this problem by selectively targeting the disease-causing lymphocytes.
- There is also interest in exploiting our knowledge of regulatory T cells (Tregs) to treat inflammatory diseases.
- Numerous clinical trials are ongoing to purify patients' Tregs, expand and activate them in culture, and transfer them back to the patients.
- Another approach is to treat patients with low doses of IL-2, which is expected to activate and maintain Tregs more than effector cells, or IL-2 that is mutated to bind preferentially to CD25, the IL-2 receptor chain that is expressed at constant and high levels in Tregs.

Therapeutic Approaches for Immunologic Diseases

Other Biologic Agents

- CTLA-4-Ig, a fusion protein of the extracellular domain of CTLA-4 and an IgG Fc region, blocks B7 costimulators and is approved for treatment of RA and graft rejection.
- Antibodies against integrins have been used to inhibit leukocyte migration into tissues, particularly the central nervous system (CNS) in MS patients (anti-VLA-4) and the intestines in IBD patients (anti-α4β7).

Systemic Lupus Erythematosus (SLE): The Prototypic Immune Complex—Mediated Disease

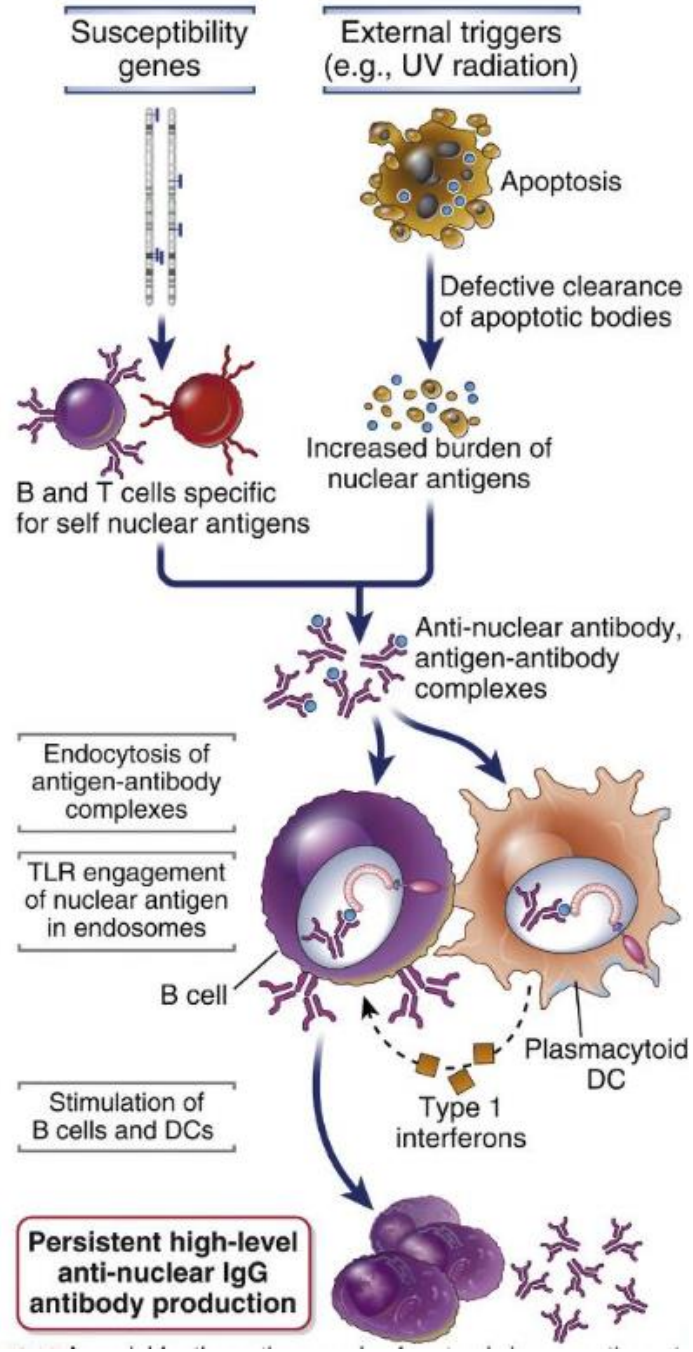
- SLE is a chronic, remitting and relapsing, multisystem autoimmune disease that affects predominantly women.
- The principal clinical manifestations are rashes, arthritis, and glomerulonephritis, but hemolytic anemia, thrombocytopenia, and neuropsychiatric disorders are also common.
- The most frequent are antinuclear, particularly anti-DNA, antibodies; others include antibodies against ribonucleoproteins, histones, and nucleolar antigens.
- Immune complexes formed from these autoantibodies and their specific antigens deposit in small arteries and capillaries throughout the body and are responsible for glomerulonephritis, arthritis, and vasculitis.
- Hemolytic anemia and thrombocytopenia are caused by autoantibodies against erythrocytes and platelets, respectively.
- The principal diagnostic test for the disease is the presence of antinuclear antibodies; antibodies against double-stranded native DNA are specific for SLE.

Systemic Lupus Erythematosus (SLE): The Prototypic Immune Complex—Mediated Disease

- A model for the pathogenesis of systemic lupus erythematosus.
- In this hypothetical model, various susceptibility genes interfere with the maintenance of self-tolerance and external triggers lead to persistence of nuclear antigens.
- The result is an antibody response against self nuclear antigens, which is amplified by the Toll-like receptor (TLR)-dependent activation of dendritic cells (DCs) and B cells by nucleic acids, and the production of type 1 interferons.

New Therapies for Systemic Lupus Erythematosus

- The recent advances in our understanding of SLE are leading to novel therapeutic attempts, but success has proven elusive.
- There has been great interest in depleting B cells by use of an antibody against the B cell surface protein CD20, but clinical trials using anti-CD20 have had little success.
- An antibody that blocks the B cell growth factor, B cell-activating factor (BAFF), is now approved for the treatment of SLE but seems to have only modest efficacy.
- Additional approaches that are being tried are to combine B cell depletion with depletion of long-lived plasma cells using proteasome inhibitors (which lead to the accumulation of misfolded proteins and ultimately cell death) and to activate Tregs by treating patients with low dose IL-2.
- Despite the involvement of IFN-a in the disease, clinical trials to test the efficacy of antibodies against IFN-a or its receptor have not been successful.



Rheumatoid Arthritis (RA)

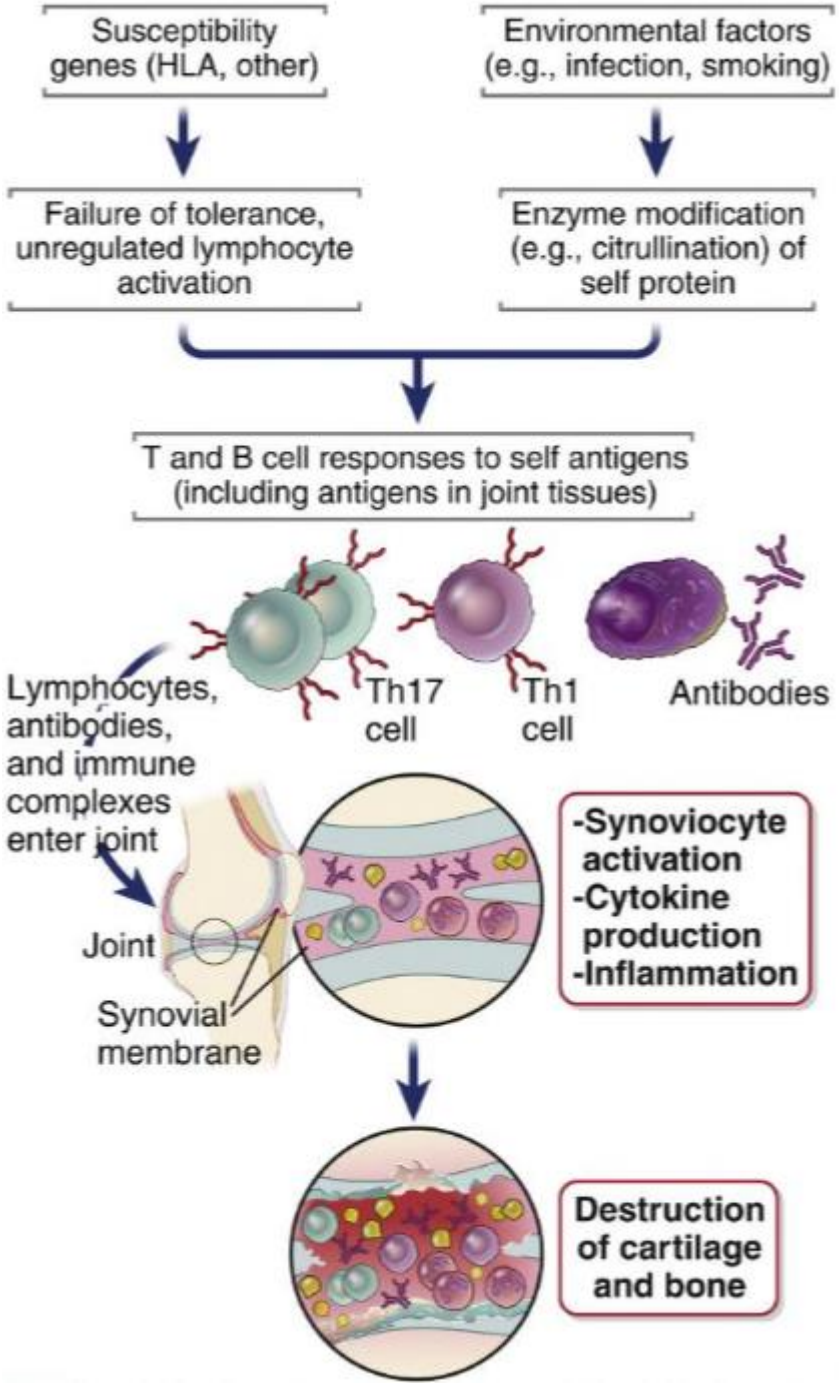
- RA is an inflammatory disease involving small and large joints of the extremities, including fingers and toes, wrists, shoulders, knees, and ankles.
- The disease is characterized by inflammation of the synovium associated with destruction of the joint cartilage and bone, with a morphologic picture indicative of a local immune response.
- Both cell-mediated and humoral immune responses may contribute to development of synovitis.
- CD4+ Thl and Th17 cells, activated B lymphocytes, plasma cells, and macrophages as well as other inflammatory cells, are found in the inflamed synovium, and in severe cases, well-formed lymphoid follicles with germinal centers (so-called tertiary lymphoid organs) may be present.
- Numerous cytokines, including IL-1, IL-8, TNF, IL-6, IL-17, and IFN-y, have been detected in the synovial (joint) fluid.
- Cytokines are thought to recruit leukocytes whose products cause tissue injury and also to activate resident synovial cells to produce proteolytic enzymes, such as collagenase, that mediate destruction of the cartilage, ligaments, and tendons of the joints.
- Increased osteoclast activity in the joints contributes to the bone destruction in RA, and this may be caused by the production of the TNF family cytokine RANK (receptor activator of nuclear factor KB) ligand by activated T cells.
- RANK ligand binds to RANK, a member of the TNF receptor family that is expressed on osteoclast precursors and induces their differentiation and activation. Systemic complications of RA include vasculitis, presumably caused by immune complexes, and lung injury with fibrosis.
- Activated B cells and plasma cells are often present in the synovia of affected joints.
- Patients frequently have circulating IgM or IgG antibodies that react with the Fc (and rarely Fab) portions of their own IgG molecules.
- These autoantibodies are called rheumatoid factors, and their presence is used as a diagnostic test for RA.
- Another type of antibody that has been detected in over half of patients is specific for citrullinated proteins.
- About 60% to 80% of RA patients have rheumatoid factor and/or ACPAs and are said to have seropositive RA, which tends to be more severe than non-seropositive RA.
- Many asymptomatic seropositive individuals have been studied and observed to gradually develop seropositive RA.
- Both types of antibodies are diagnostic markers and may be involved in the formation of pathogenic immune complexes.

Rheumatoid Arthritis (RA)

- A model for the pathogenesis of rheumatoid arthritis.
- According c this model, citrullinated proteins induced by environmental stimuli elicit T cell and antibody responses in genetically susceptible individuals.
- The T cells and antibodies enter joints, respond to the self proteins, and cause tissue injury mainly by cytokine secretion and perhaps also by antibody-dependent effector mechanisms.
- Protein modifications other than citrullination may lead to the same result. HLA, Human leukocyte antigen.

New Therapies for Rheumatoid Arthritis

- The realization of the central role of T cells and cytokines in the disease has led to remarkable advances in treatment, in which specific molecules have been targeted on the basis of scientific understanding.
- Chief among these new therapies are antagonists of TNF, which have transformed the course of the disease in many patients from one of progressive and inexorable joint destruction to one of smoldering but manageable chronic inflammation.
- Blockade of cytokines other than TNF has been effective, including an antibody that blocks the IL-6 receptor, an IL-1 antagonist, and a small molecule that inhibits JAK signaling.
- Inhibition of T cell activation has been accomplished by blockade of B7:CD28 costimulation with CTLA-4-Ig.
- B cell depletion with antiCD20 antibody has also proven to be efficacious, although the mechanisms underlying this effect are not well understood.



Type 1 Diabetes

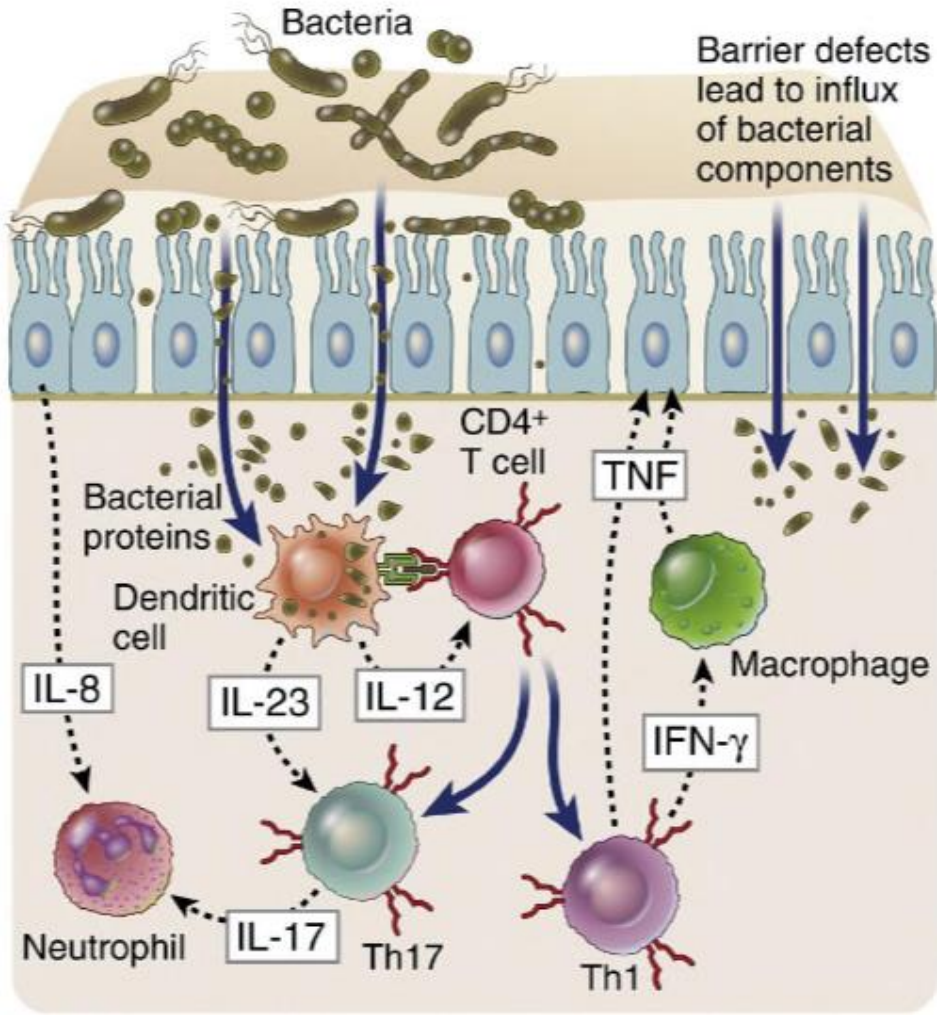
- Type 1 diabetes, previously called insulin-dependent diabetes, is a multisystem metabolic disease resulting from impaired insulin production, with a peak onset at 11 to 12 years of age.
- The incidence of the disease appears to be increasing in North America and Europe.
- The disease is characterized by hyperglycemia and ketoacidosis.
- Chronic complications of diabetes include progressive atherosclerosis of arteries, which can lead to ischemic necrosis of limbs and internal organs, and microvascular obstruction causing damage to the retina, renal glomeruli, and peripheral nerves.
- Type 1 diabetes is caused by a deficiency of insulin resulting from immune-mediated destruction of the insulin-producing B cells of the islets of Langerhans in the pancreas, and continuous hormone replacement therapy is needed.
- There is usually a long lag of many years between the initiation of autoimmunity and overt clinical disease because 90% or more of the islets have to be destroyed before clinical manifestations are seen.

Type 1 Diabetes

- Several mechanisms may contribute to B cell destruction, including inflammation mediated by CD4+ Th1 cells reactive with islet antigens (including insulin), CTL-mediated lysis of islet cells, local production of cytokines (TNF and IL-1) that damage islet cells, and autoantibodies against islet cells.
- In the few cases in which the pancreatic lesions have been examined at the early active stages of the disease, the islets show cellular necrosis and lymphocytic infiltration consisting of both CD4+ and CD8+ T cells.
- This lesion is called insulitis.
- Autoantibodies against islet cells and insulin are also detected in the blood of these patients.
- In susceptible children who have not developed diabetes (such as relatives of patients), the presence of antibodies against islet cells is predictive of the development of type 1 diabetes.
- Multiple genes are associated with type 1 diabetes.
- Most attention has been focused on the role of HLA genes.
- Between 90% and 95% of Caucasians with type 1 diabetes have HLA-DR3 or DR4, or both, in contrast to about 40% of healthy subjects, and 40% to 50% of patients are DR3/DR4 heterozygotes, in contrast to 5% of healthy subjects.
- The actual HLA genes that may play a role in the pathogenesis may be HLA-DQ alleles that are in linkage disequilibrium with the DR alleles. Several non-HLA genes also contribute to the disease.
- The first of these to be identified is insulin, with tandem repeats in the promoter region being associated with disease susceptibility.

Inflammatory Bowel Disease

- IBD is a heterogeneous group of disorders characterized by chronic remitting inflammation in the small or large bowel that is likely a result of inadequately regulated responses to commensal bacteria.
- The two main types of IBD are Crohn's disease, which can affect the entire thickness of the wall in any part of the gastrointestinal tract but most frequently involves the terminal ileum, and ulcerative colitis, which is restricted to the colonic mucosa.
- Defects in innate immunity to gut commensals. Loss-of-function mutations in the gene that encodes the NOD2 cytoplasmic innate immune sensor are associated with a subset of Crohn's disease and may lead to reduced innate defenses against intestinal microbes.
- Abnormal Th17 and Th1 responses. Analysis of T cell responses in animal models and patients with IBD indicates that there is an active Th17 response in the affected parts of the bowel.
- Defective function of regulatory T cells. It is possible that IBD may be caused by inadequate Treg-mediated suppression of immune responses to commensal organisms.
- Polymorphisms of genes that are associated with macroautophagy and the unfolded protein response to endoplasmic reticulum stress are risk factors for IBD.



Inflammatory Bowel Disease

Immunotherapies for IBD

- TNF antagonists were the first biologic agent used to treat IBD.
- The findings of exaggerated Th1 and Th17 responses are the basis for treating patients with a monoclonal antibody that binds a polypeptide (p40) shared by IL-23 and IL-12.
- IL-23 is required for Th17-mediated immune responses, and IL-12 is required for Th1 responses.
- Clinical trials of IL-17 antagonist treatment for Crohn's disease have not shown efficacy, suggesting that excessive production of IL-17 may not, by itself, be responsible for this disorder.
- Another biologic agent approved for Crohn's disease is a monoclonal antibody specific for the α4β7 integrin, which is expressed on gut-homing lymphocytes.

Psoriasis

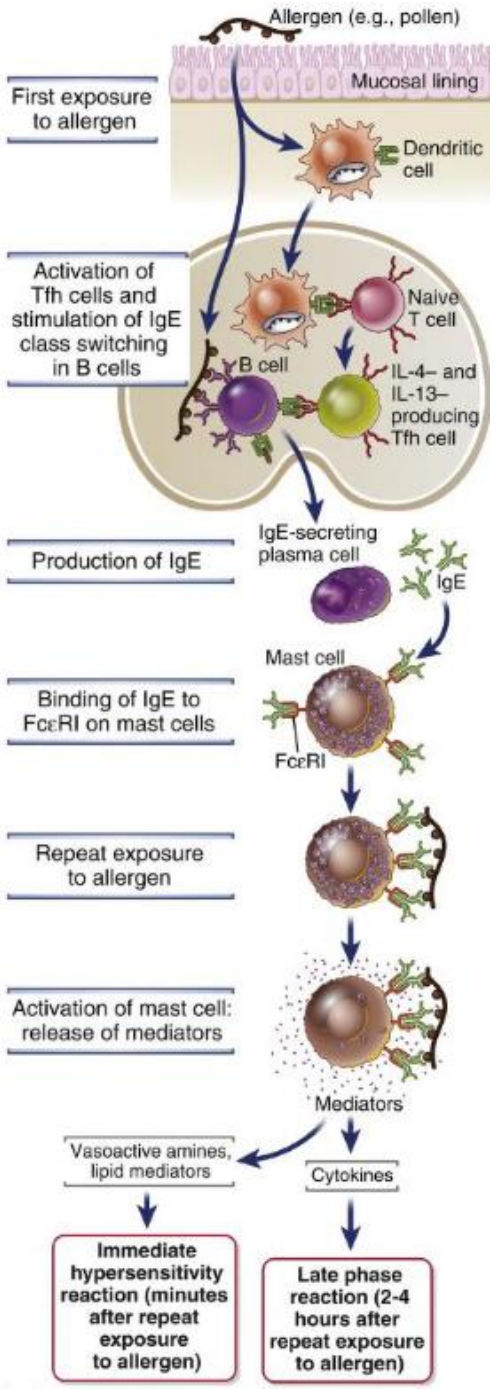
- Psoriasis is the prototypic IL-17-mediated chronic inflammatory autoimmune disease.
- It involves primarily the skin and also affects the joints and other tissues in some cases.
- The responsible self antigens are not clearly defined, but possible candidates include cathelicidin (an antimicrobial protein) and a keratin, both produced by keratinocytes, and other proteins made by melanocytes.
- The autoimmune response may be triggered by infection or other unknown stimuli.
- High levels of IL-17 and the Th17-inducing cytokine IL-23 are found in psoriatic lesions, as are large numbers of IL-17-producing CD4+ and CD8+ T cells.
- The contribution of IL-17-producing γδ T cells and ILCs has been suggested but not clearly established. Genome-wide association studies have revealed disease-associated polymorphisms in the IL-23 receptor gene and other genes associated with Th17 development.
- It is postulated that once IL-17-producing T cells are activated, presumably by one or more self antigens, the IL-17 they produce stimulates inflammation and activates DCs to produce TNF and other, Th17-inducing cytokines.
- This reaction sets up a vicious cycle of continuing inflammation.
- Effective new biologic therapies have been developed based on this model.
- The first such agents to be used in the disease were TNF antagonists.
- These were followed by an antibody specific for the p40 chain that is shared by IL-12 and IL-23, mentioned earlier in the therapy of IBD.
- The most successful of these biologic agents are antibodies that block IL-17 or IL-23, which are very effective in most patients.

Allergy

Prof. Roberto Ria

Overview of IgE-Dependent Allergic Reactions

- Allergy is the prototypic type 2 inflammatory disease, mediated by the cytokines IL-4, IL-5, and IL-13, different combinations of which are secreted by Th2 cells, T follicular helper (Tfh) cells, ILC2s, and a few other cell types.
- The cytokine responses of these cells are often collectively called type 2 immune responses.
- A hallmark of allergic diseases is the production of IgE antibody, which depends on the activation of IL-4- and IL-13-producing helper T cells.
- Allergic reactions require previous T cell-dependent allergen-specific IgE production by B cells and the binding of the IgE to mast cells.
- The clinical and pathologic manifestations of allergy consist of the vascular and smooth muscle reactions that develop rapidly after allergen challenge in a sensitized individual (immediate hypersensitivity) and a delayed late-phase inflammatory reaction.
- Allergic reactions are manifested in different ways, depending on the tissues affected, including skin rashes, sinus and nasal congestion, inflamed conjunctiva, bronchial constriction with difficulty in breathing, abdominal pain, diarrhea, and shock.
- In the most extreme systemic form, called anaphylaxis, mast cell-derived mediators can restrict airways to the point of asphyxiation and produce cardiovascular collapse leading to shock, which together may result in death.
- The development of allergies is the result of complex and poorly understood gene-environment interactions.



Production of IgE

- Atopic individuals produce high levels of IgE in response to environmental allergens, whereas normal individuals generally produce other Ig isotypes, such as IgM and IgG, and only small amounts of IgE.
- The most successful of these biologic agents are antibodies that block IL-17 or IL-23, which are very effective in most patients.

The Nature of Allergens

- Antigens that elicit immediate hypersensitivity reactions (allergens) are proteins or chemicals bound to proteins.
- Typical allergens include proteins in pollen, house dust mites, animal dander, foods, and drugs.

Activation of Type 2 Cytokine-Producing Helper T Cells

- The development of allergic disease begins with the differentiation of IL-4-, IL-5-, and IL-13-producing CD4 + helper T cells in lymphoid tissues.

Activation of B Cells and Switching to IgE

- B cells specific for allergens are activated by Tfh cells in secondary lymphoid organs, as in other T cell-dependent B cell responses.
- In response to CD40 ligand and cytokines, mainly IL-4 and IL-13, produced by these helper T cells, the B cells undergo heavy chain isotype switching and produce IgE.

Cells Involved in Allergic Reactions

- The major effector cells of immediate hypersensitivity reactions and allergic disease are type 2 cytokine-secreting cells (Th2 cells, Tfh cells, and possibly ILC2s), mast cells, basophils, and eosinophils.

Role of Th2 Cells and Innate Lymphoid Cells in Allergic Disease

- Th2 cells and ILC2s secrete cytokines, including IL-4, IL-5, and IL-13, which promote inflammatory responses to allergens within tissues.
- IL-4 secreted by Th2 cells induces expression of endothelial VCAM-1 (vascular cell adhesion molecule 1), which promotes the recruitment of eosinophils and additional Th2 cells into tissues.
- IL-5 secreted by Th2 cells enhances eosinophil production in the bone marrow and activates mature eosinophils in tissues. IL-13 stimulates epithelial cells (e.g., in the airways) to secrete increased amounts of mucus, and excessive mucus production is also a common feature of these reactions.
- Consistent with a central role of Th2 cells in immediate hypersensitivity, more allergen-specific IL-4-secreting T cells are found in the blood of atopic individuals than in nonatopic persons.
- In atopic patients, the allergen-specific T cells also produce more IL-4 per cell than in normal individuals.
- Accumulations of Th2 cells are found at sites of immediate hypersensitivity reactions in the skin and bronchial mucosa.
- ILC2s produce many of the same cytokines as Th2 cells, specifically IL-5 and IL-13, and therefore may have similar roles in allergic reactions.
- Because ILCs normally reside in tissues, their cytokines may contribute to early allergic inflammation before Th2 cells are generated and migrate to the tissues.
- The ILC2s may also work in concert with Th2 cells later, to sustain inflammation.

Cells Involved in Allergic Reactions

Properties of Mast Cells and Basophils

- Activated mast cells secrete a variety of mediators that are responsible for the manifestations of allergic reactions.
- Basophils are blood granulocytes with structural and functional similarities to mast cells.

Binding of IgE to Mast Cells and Basophils: the Fcε Receptor

- Mast cells and basophils express a high-affinity Fc receptor specific for ε heavy chains, called Fc ε RI, which binds IgE.
- Each FcεRI molecule on mast cells is composed of an α chain that binds the Fc region of IgE and a B chain and two y chains that are responsible for signaling.

Activation of Mast Cells

- Mast cells are activated by cross-linking of FcεRI molecules, which occurs by binding of multivalent antigens to the IgE molecules that are attached to the Fc receptors.
- Activation of mast cells results in three types of biologic responses: secretion of preformed granule contents by exocytosis (degranulation), synthesis and secretion of lipid mediators, and synthesis and secretion of cytokines.

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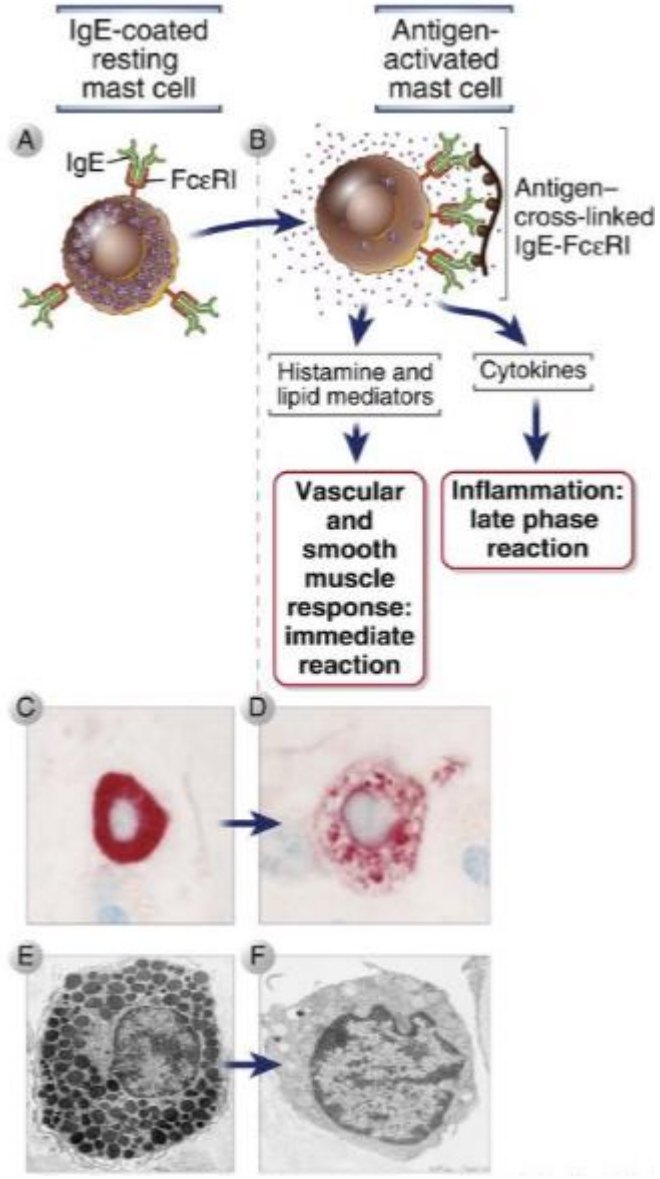
Cells Involved in Allergic Reactions

Mast cell activation.

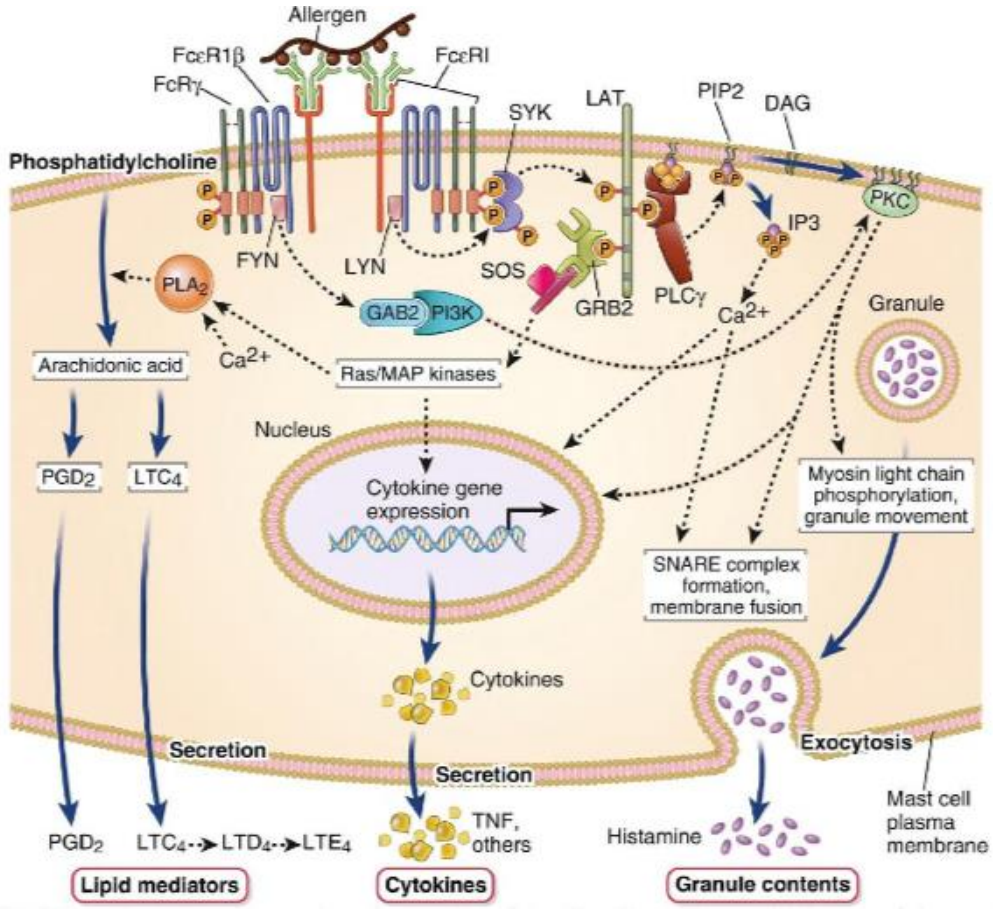
- Antigen binding to immunoglobulin E IgE cross-links FcεRI molecules on mast cells, which induces the release of mediators that cause the hypersensitivity reaction (A and B).
- Other stimuli, including the complement fragment Toll-like receptor (TLR) ligands, the complement fragment C5a, cytokines, neuropeptides, and cationic secretagogue, can also activate mast cells independent of FcεRI.
- A photomicrograph of a resting mast cell with abundant purple-staining cytoplasmic granules is shown in C.
- These granules are also seen in the electron micrograph of a resting mast cell shown in E.
- In contrast, the depleted granules of an activated mast cell are shown in the photomicrograph (D) and electron micrograph (F).



Cells Involved in Allergic Reactions

Biochemical events of mast cell activation.

- Cross-linking of bound immunoglobulin E by antigen promotes LYN phosphorylation of other signaling molecules, which leads to activation of protein tyrosine kinase SYK, which in turn causes activation of a mitogen-activated protein (WAP) kinase cascade and phospholipase Cy (PLCy).
- PLCy catalyzes the release of inositol trisphosphate (IP3) and diacylglycerol (DAG) from membrane phosphatidylinositol 4,5bisphosphate (PIP2).
- IP3 causes release of intracellular calcium from the endoplasmic reticulum.
- Calcium and DAG activate protein kinase C (PKC).
- FYN phosphorylation of GAB2 leads to PI3K activation, which contributes to PKC activation.
- Calcium, MAP kinases, and PKC promote cytokine gene transcription, leading to secretion of cytokines.
- PKC and calcium also enhance granule exocytosis, releasing histamine and other preformed mediators.
- Calcium and MAP kinases combine to activate the enzyme cytosolic phospholipase A2 (PLA 2), which initiates the synthesis of lipid mediators, including prostaglandin D2 (PGD 2) and leukotriene C4 (LTC 4).



Cells Involved in Allergic Reactions

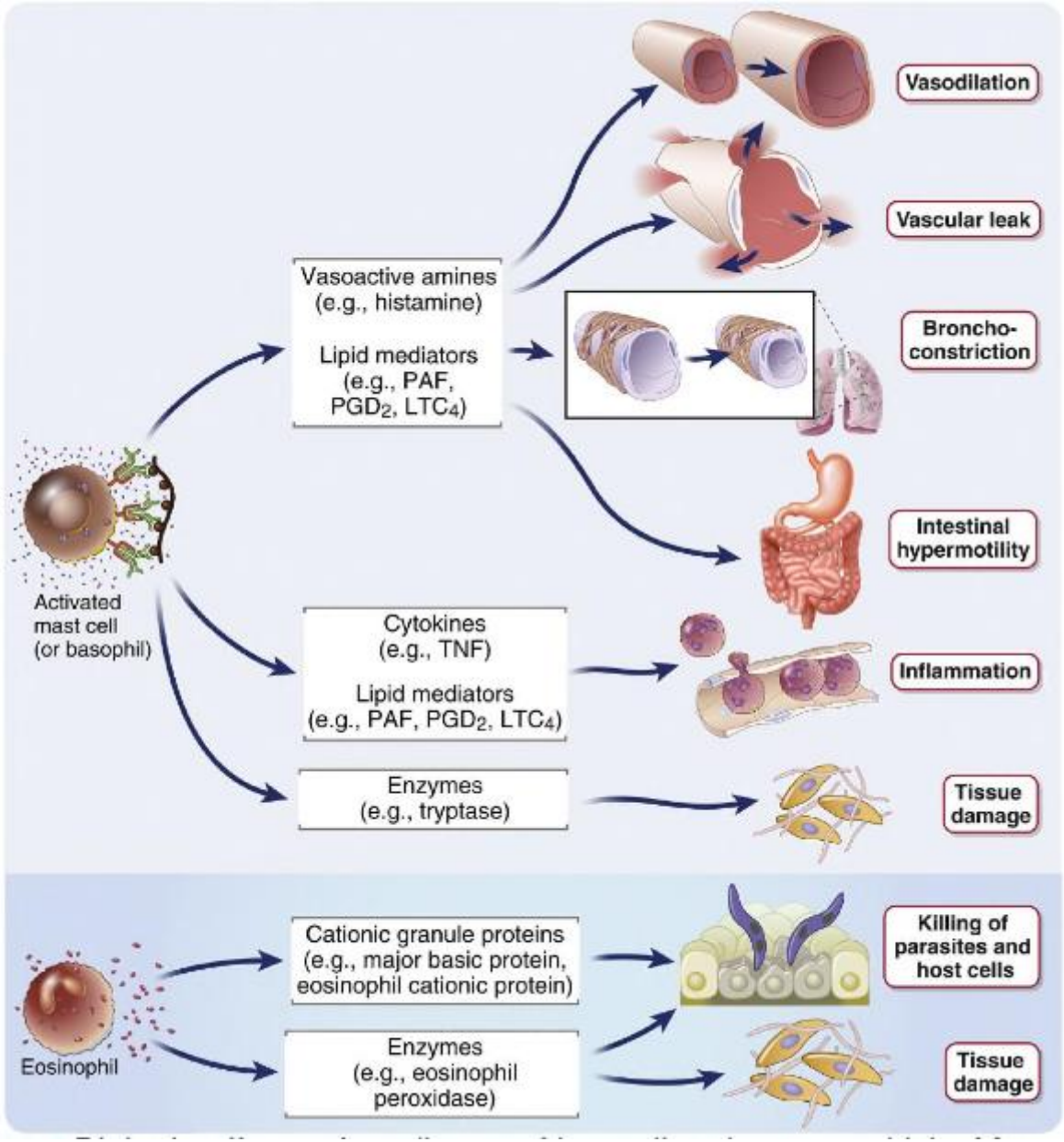
Mediators Derived From Mast Cells.

- The effector functions of mast cells are mediated by soluble molecules released from the activated cells.
- **Vasoactive Amines**. Many of the biological effects of mast cell activation are mediated by vasoactive amines that are released from cytoplasmic granules and act on blood vessels and smooth muscle.
- The major mediator of this class is histamine, but serotonin may also be important.
- **Granule Enzymes and Proteoglycans**. Neutral serine proteases, including tryptase and chymase, are the most abundant protein constituents of mast cell secretory granules and may contribute to tissue damage in immediate hypersensitivity reactions.
- **Lipid Mediators**. Mast cell activation results in the rapid de novo synthesis and release of lipid mediators that have a variety of effects on blood vessels, bronchial smooth muscle, and leukocytes.
- The major arachidonic acid-derived mediator produced by the cyclooxygenase pathway in mast cells is prostaglandin D2 (PGD2).
- The major arachidonic acid-derived mediators produced by the lipoxygenase pathway are the leukotrienes, especially LTC4 and its degradation products LTD4 and LTE4, called cysteinyl leukotrienes.
- **Cytokines**. Mast cells produce many cytokines contributing to allergic inflammation (the late-phase reaction). These cytokines include TNF, IL-1, IL-4, IL-5, IL-6, IL-9, IL-13, CCL3, CCL4, and various colony-stimulating factors, such as IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF).

Cells Involved in Allergic Reactions

Biologic effects of mediators of immediate hypersensitivity.

- Mast cell and basophil mediators include vasoactive amines and enzymes stored preformed in granules, as well as cytokines and lipid mediators, which are largely newly synthesized on cell activation.
- The biogenic amines and lipid mediators induce vascular leakage, bronchoconstriction, and intestinal hypermotility, all components of the immediate response.
- Cytokines and lipid mediators contribute to inflammation, which is part of the late-phase reaction.
- Enzymes probably contribute to tissue damage.
- Activated eosinophils release preformed cationic proteins and enzymes that are toxic to parasites and host cells.
- Some eosinophil granule enzymes probably contribute to tissue damage in chronic allergic diseases.

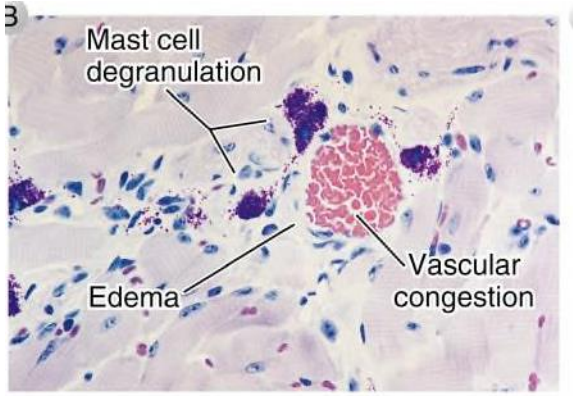


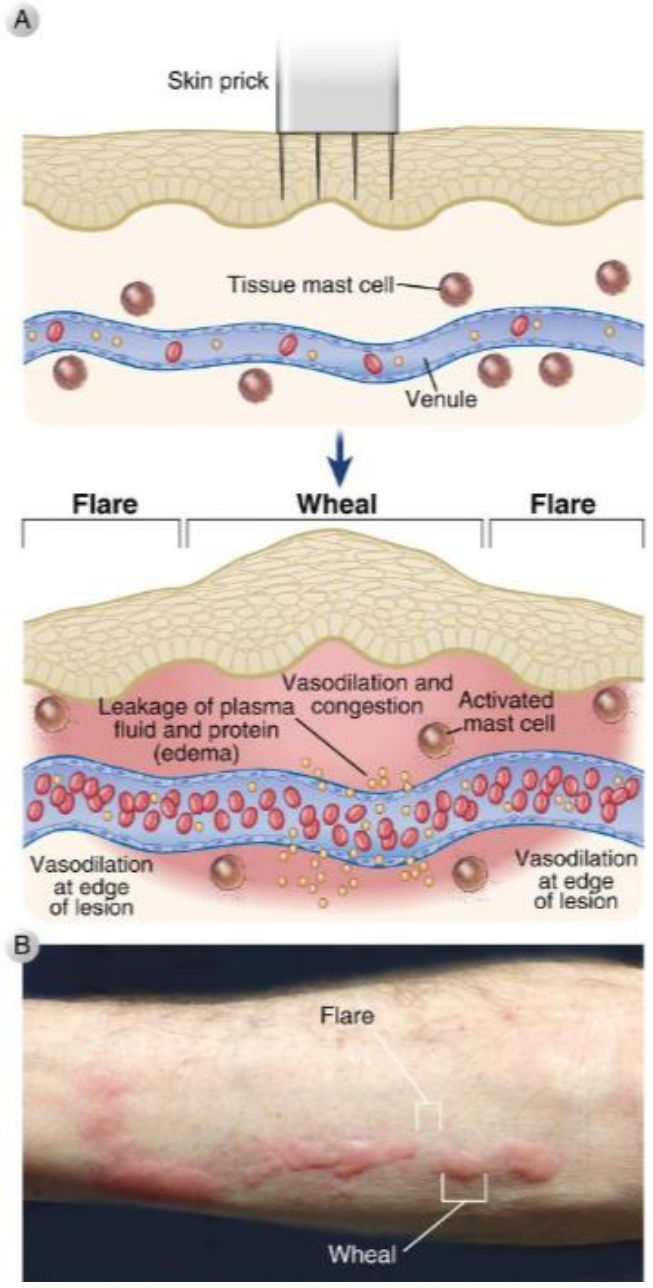
Cells Involved in Allergic Reactions

Properties of Eosinophils.

- Eosinophils are bone marrow-derived granulocytes that are abundant in the inflammatory infiltrates of late-phase reactions and are involved in many of the pathologic processes in allergic diseases.
- Cytokines produced by Th2 cells and ILC2s promote the activation of eosinophils and their recruitment to late-phase reaction sites.
- Upon activation, eosinophils release granule proteins that are toxic to microbes and may injure normal tissues.

Reactions Dependent on IgE and Mast Cells

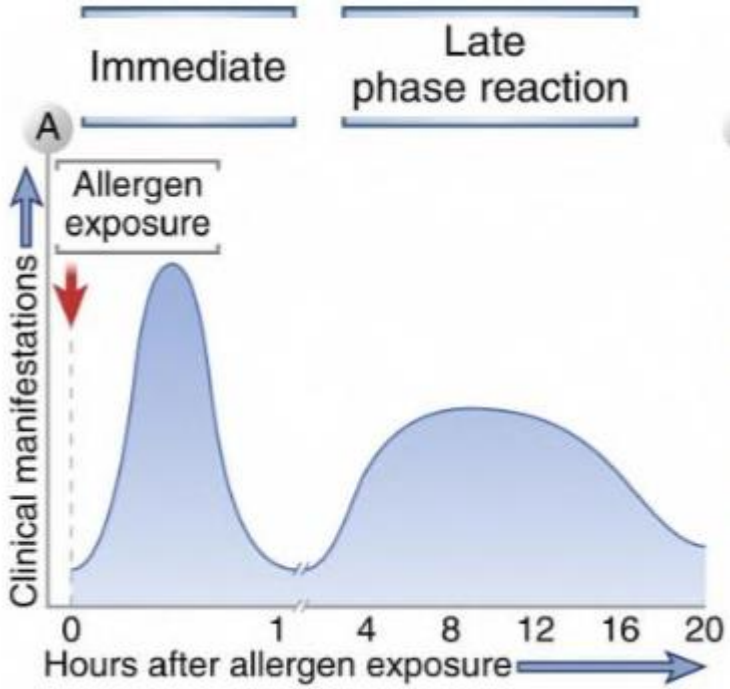




The Immediate Reaction.

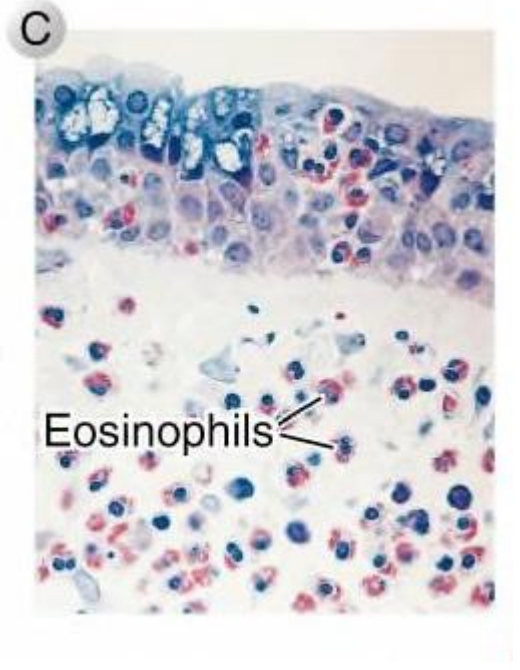
- The early vascular changes that occur during immediate hypersensitivity reactions are demonstrated by the wheal-and-flare reaction to intradermal injection of an allergen.
- When an individual who has previously encountered an allergen and produced IgE antibody is challenged by intradermal injection of the same antigen, the injection site becomes red from locally dilated blood vessels engorged with red blood cells.
- The site then rapidly swells as a result of leakage of plasma from the venules. This soft swelling is called a wheal and can involve an area of skin as large as several centimeters in diameter.
- Subsequently, blood vessels at the margins of the wheal dilate and become engorged with red blood cells, producing a characteristic red rim called a flare.
- The full wheal-and-flare reaction can appear within 5 to 10 minutes after administration of antigen and usually subsides in less than 1 hour.
- The wheal-and-flare reaction is dependent on IgE and mast cells.
- Histologic examination shows that mast cells in the area of the wheal-and flare have discharged their cytoplasmic granules (i.e., released their preformed mediators).

Reactions Dependent on IgE and Mast Cells



The Late-Phase Reaction.

- The immediate wheal-and-flare reaction is followed 2 to 4 hours later by a late-phase reaction consisting of the accumulation of inflammatory leukocytes, including neutrophils, eosinophils, basophils, and helper T cells.
- The late-phase reaction may occur without a detectable preceding immediate hypersensitivity reaction.
- Bronchial asthma is a disease in which there may be repeated bouts of inflammation with accumulations of eosinophils and Th2 cells without the vascular changes that are characteristic of the immediate response.
- In such disorders, there may be little mast cell activation, and the cytokines that sustain the late-phase reaction may be produced mainly by T cells.



Genetic Susceptibility to Allergic Disease

- The propensity to develop allergies is influenced by the inheritance of several genes.
- Atopic disease often affects several members of the same family, and studies have shown autosomal transmission of atopy, but the full inheritance pattern is multigenic.
- Within the same family, the target organ of atopic disease is variable.
- Different gene variants that confer increased susceptibility to asthma and other atopic diseases have been identified.
- One of the first significant findings from genetic allergy studies was the identification of a susceptibility locus for atopy on chromosome 5q, near the site of the gene cluster encoding the cytokines IL-4, IL-5, IL-9, and IL-13.
- Mutations that result in loss of expression or function of the protein filaggrin result in a significant risk for the development of atopic dermatitis in early childhood and subsequent allergic diseases, including asthma.
- Some genes whose products regulate the innate immune response to infections have been associated with allergy and asthma.
- These include CD14, a component of the lipopolysaccharide receptor, and TLR2 and TLR4.

Environmental Factors in Allergy

- It is clear that environmental influences have a significant impact on the development of allergies, and they synergize with genetic risk factors.
- Environmental influences include exposure to allergens themselves, to infectious organisms, and possibly other factors that have an impact on mucosal barrier function, such as air pollution.
- Furthermore, the time of life when exposure to these environmental factors occurs, especially early life exposure, appears to be important.
- Exposure to microbes during early childhood may reduce the risk of developing allergies.
- The hygiene hypothesis was proposed, which states that early-life and even perinatal exposure to environmental and commensal microbes and infections lead to a regulated maturation of the immune system and perhaps early development of regulatory T cells.
- Respiratory viral and bacterial infections are a predisposing factor in the development of asthma and exacerbations of preexisting asthma.
- This may seem contradictory to the hygiene hypothesis, but these asthma-associated infections are due to human pathogens that may damage pulmonary mucosal barriers; the data supporting the hygiene hypothesis focus on exposure to a broad range of environmental bacteria not necessarily related to tissue injury.

Allergic Diseases in Humans: Pathogenesis and Therapy

- The manifestations of allergic diseases depend on the tissues in which the mast cell mediators and type 2 cytokines have effects, as well as the chronicity of the resulting inflammatory process.
- Frequently, an individual will develop more than one atopic disorder.
- The clinical presentation of atopic dermatitis in babies followed later in childhood by allergic rhinitis and asthma is known as the atopic march, and these three conditions, described later, are called the atopic triad.
- **Systemic Anaphylaxis**: Anaphylaxis is a systemic immediate hypersensitivity reaction characterized by edema in many tissues and a decrease in blood pressure secondary to vasodilation and vascular leak.
- These effects usually result from the systemic presence of antigen introduced by injection, an insect sting, or absorption across an epithelial surface such as gut mucosa.
- The allergens that most often cause anaphylaxis include penicillin family antibiotics and proteins in peanuts, tree nuts, fish, shellfish, milk, eggs, and bee venom, but there are many other drugs, food, and environmental culprits.
- The allergen activates mast cells in many tissues, resulting in the release of mediators that gain access to vascular beds throughout the body.
- The decrease in vascular tone and leakage of plasma caused by mast cell mediators can lead to a significant decrease in blood pressure, or shock, called anaphylactic shock, which is often fatal.
- Mast cell mediators may impair breathing by causing laryngeal edema, bronchoconstriction and excess bronchial mucus production.
- There is often diarrhea due to intestinal hypermotility, outpouring of mucus in the gut, and urticarial lesions (hives) in the skin.
- Anaphylaxis usually occurs within seconds to an hour of exposure to an allergen. In about 20% of patients, a second recurrence of symptoms is seen without known re-exposure to the allergen, up to 12 hours after the first episode.
- This is often called a late-phase anaphylactic reaction but should not be confused with the late-phase reaction to allergen discussed earlier. It is unknown which mast cell mediators are the most important in anaphylactic shock.
- The mainstay of treatment is epinephrine injection, which can be lifesaving by reversing mast cell mediators' broncho constrictive and vasodilatory effects. Epinephrine also improves cardiac output, further aiding survival from threatened circulatory collapse. Antihistamines are often given to patients with anaphylaxis, but their effectiveness is not proved.

Immediate Hypersensitivity Reactions in the Upper Respiratory Tract, Gastrointestinal Tract, and Skin

- **Allergic rhinitis**: also called hay fever, is perhaps the most prevalent allergic disease and is a consequence of immediate hypersensitivity reactions to common allergens such as plant pollen or house dust mites localized to the upper respiratory tract by inhalation.
- The pathologic and clinical manifestations include mucosal edema, leukocyte infiltration with abundant eosinophils, mucus secretion, coughing, sneezing, and difficulty breathing.
- Allergic conjunctivitis with itchy eyes is commonly associated with the rhinitis. Focal protrusions of the nasal mucosa, called nasal polyps, filled with edema fluid and eosinophils may develop in patients who have frequent repetitive bouts of allergic rhinitis.
- Antihistamines are commonly used to treat allergic rhinitis.

Immediate Hypersensitivity Reactions in the Upper Respiratory Tract, Gastrointestinal Tract, and Skin

- **Food allergies**: are immediate hypersensitivity reactions to ingested foods that lead to the release of mediators from intestinal mucosal and submucosal mast cells of the gastrointestinal tract, including the oropharynx.
- The resulting clinical manifestations include pruritus, tissue edema, enhanced peristalsis, increased epithelial fluid secretion, and symptoms of oropharyngeal swelling, vomiting, and diarrhea.
- Rhinitis, urticaria, and mild bronchospasm are also often associated with allergic reactions to food, suggestive of systemic antigen exposure, and anaphylaxis may occasionally occur.
- Individuals may be sufficiently sensitive to these allergens that severe systemic reactions can occur in response to small accidental ingestions.
- Allergies to foods, including cow's milk, eggs, peanuts, tree nuts, shellfish, fish, soy, and wheat, are extremely common across the world.
- Common allergic reactions in the skin include urticaria and atopic dermatitis.
- **Urticaria**, or hives, is an acute wheal-and-flare reaction induced by mast cell mediators and occurs in response to direct local contact with an allergen or after an allergen enters the circulation.
- Because the reaction that ensues is mediated largely by histamine, antihistamines can attenuate this response and are the mainstay of therapy.
- Urticaria may persist for several hours or days. Rare cases of chronic urticaria are due to IgG autoantibodies specific for FcεR1 or the Fc portion of IgE.

Immediate Hypersensitivity Reactions in the Upper Respiratory Tract, Gastrointestinal Tract, and Skin

- **Atopic dermatitis**: (commonly called **eczema**) is characterized by acute flares of itchy red exudative papules and chronically dry scaly skin.
- It is part of the atopic triad (atopic dermatitis, allergic rhinitis, and asthma) discussed earlier, but it can also occur in isolation.
- It is a common skin disorder, sometimes associated with filaggrin mutations that result in defective skin barrier function.
- As a result, there is increased exposure to environmental antigens and activation of keratinocytes to secrete cytokines that promote type 2 immune responses.
- Patients with eczema go on to develop chronic late-phase reactions in the skin.
- As may be expected for a cytokine-mediated response, the late-phase inflammatory reaction is not inhibited by antihistamines but can be treated with corticosteroids, which inhibit cytokine synthesis.
- Anti-IL-4R antibody is approved for the treatment of atopic dermatitis and chronic urticaria.

Specific Immunotherapy (Desensitization) for Allergic Diseases

- In addition to therapy aimed at the consequences of immediate hypersensitivity, clinical immunologists often try to reduce the onset of allergic reactions by altering the allergen-specific immune response in the patient.
- Several empirical immunotherapy protocols have been used, which induce multiple immunologic alterations that may account for the clinical benefit.
- In one approach, called desensitization, or specific allergen immunotherapy, small quantities of the allergen are repeatedly administered subcutaneously or sublingually.
- As a result of this treatment, specific IgE levels decrease and IgG titers often rise, perhaps further inhibiting IgE production by neutralizing the antigen and by antibody feedback.
- It is possible that desensitization may work by inducing specific T cell tolerance, by changing the predominant phenotype of antigen-specific T cells from Th2 to Thl1, by inducing production of non-allergy isotypes of IgG specific for the allergen, or by inducing allergen-specific regulatory T cells; however, there is no clear evidence to support any of these hypotheses.
- The beneficial effects of desensitization may occur in a matter of hours, much earlier than changes in IgE levels.
- Although the precise mechanism is unknown, this approach has effectively prevented acute anaphylactic responses to protein antigens (e.g., insect venom) or vital drugs (e.g., penicillin).
- Many people with more common chronic atopic conditions, such as hay fever and asthma, also benefit from desensitization therapy, but the overall effectiveness for allergic disorders is more variable.
- It is now possible to identify the allergens that bind to IgE in each patient, using chip-based antibody-binding assays, and this may greatly facilitate the development of antigen-specific immunotherapy.

The Protective Roles of Immune Reactions Mediated by IgE and Mast Cells

- Although IgE- and mast cell-mediated reactions are implicated mostly in immediate hypersensitivity, it is reasonable to assume that these responses have evolved because they provide protective functions.
- The correlation of some infections with elevated IgE levels and eosinophilia supports this assumption.
- IgE- and mast cell-mediated responses are important for defense against certain types of infection.
- IgE-initiated immune reactions may contribute to the eradication of various microbes, including helminthic parasites.
- Eosinophil-mediated killing of helminths is an effective defense against these organisms.
- The activities of IL-4 and IL-13 in IgE production and IL-5 in eosinophil activation contribute to a coordinated defense against helminths.
- In addition, IgE-dependent mast cell activation in the gastrointestinal tract promotes the expulsion of parasites by increasing peristalsis and by an outpouring of mucus.
- Nonetheless, the role of type 2 responses in protecting humans from helminths is controversial, and human worm infections are frequently sustained for decades in the face of chronic type 2 responses.
- Mast cells play an important protective role as part of the innate immune response to bacterial infections and venoms.
- Mast cells can be activated by IgE-independent mechanisms in the course of an acute bacterial infection and that the mediators they release are critical for clearing the infection.
- The protective role of mast cells in this setting is mediated by TNF and depends on TNF-stimulated influx of neutrophils into the peritoneum, specifically the late-phase reaction.
- The mechanisms by which mast cells are activated during innate immune responses to bacterial infection include binding of pathogen-associated molecular patterns to TLRs on mast cells and complement activation by the alternative pathway, leading to the release of C5a, which directly triggers mast cell degranulation.
- Mast cell-derived proteases have been shown to destroy some snake and insect venoms in mice, and venom-specific IgE confers protection from envenomation.
- This is an unusual form of immunity against a potentially lethal encounter with nonmicrobial organisms and their toxins.