Hypersensitivities

The immune reactions that protect us from infection can also inflict a great deal of damage to our own cells and tissues. The immune response uses multiple strategies to reduce damage to self by turning off responses once pathogen is cleared, and by avoiding reactions to self antigens. However, these checks and balances can break down, leading to immune mediated reactions that are more detrimental than protective.

Under certain circumstances the imfammatory responses can have deleterious effects, resulting in tissue injury, serious diseases or even death.

Such an inappropriate and damaging immune response is termed **hypersensitivity**.

1. Immune system could respond inappropriately to antigenic challenge was recognized in the twentieth century.

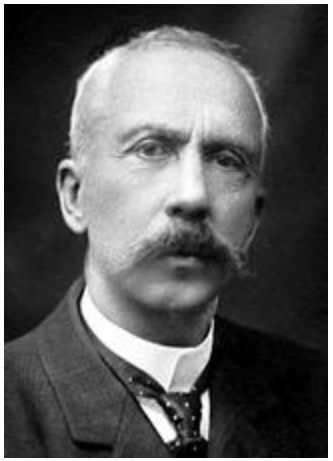
2. Paul Portier and Charles Richet, two French Scientists investigated the problem of bathers in Mediterranean reacting violently to the stings of Portuguese man-of-war jellyfish.

3. They isolated the toxin and prepared vaccines and tested on dogs. They injected the toxins to dogs and also introduced a booster dose.

4. Instead of reacting to the booster by producing antibodies, the dogs reacted with vomiting , diarrhea, asphyxia, and death.

5. Thus, the sensitized animal overreacted to the antigen.

6. Richet coined the term anaphylaxis, derived from the Greek and translated loosely as “against protection” to describe this overreaction of the immune system, the first description of a hypersensitivity reaction. Richet was subsequently awarded the Nobel Prize in Physiology or Medicine in 1913.



Charles Richet

The Nobel Prize in Physiology or Medicine 1913

Born: 26 August 1850, Paris, France

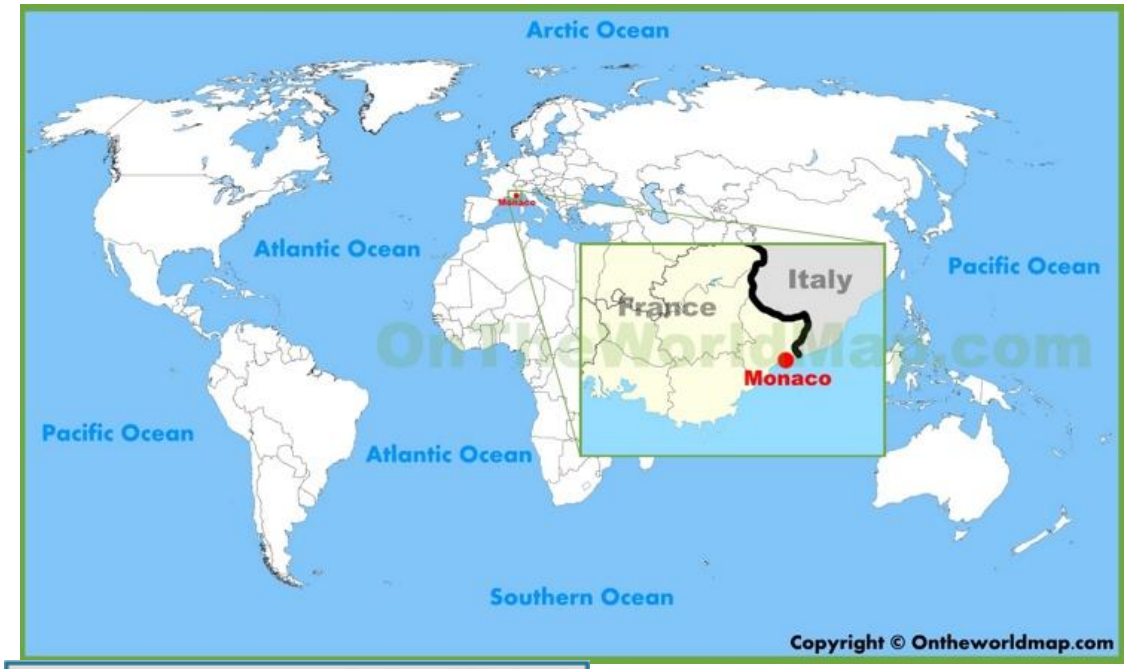
Died: 4 December 1935, Paris, France

Affiliation at the time of the award: Sorbonne University, Paris, France

Prize motivation: "**in recognition of his work on anaphylaxis**".

Field: immunity

Prize share: 1/1



During a cruise on the yacht of **Prince Albert of Monaco**, the Prince advised Charles Richet to study *Physalia* poison. Together with his friends Georges Richard and Paul Portier they found that it was easily dissolved in glycerol and that by injecting this glycerol solution, the symptoms of *Physalia* poisoning were reproduced.

Portuguese man-of-war jellyfish (*Physalia physalis*)

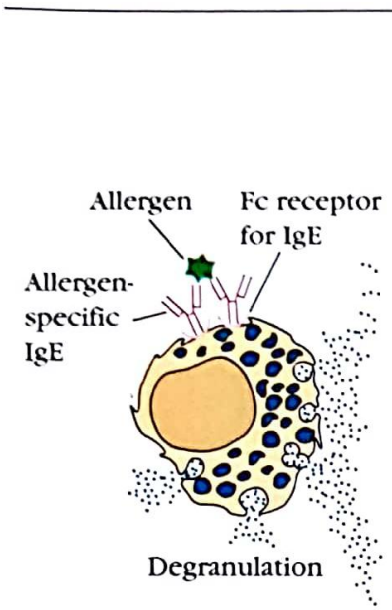
1. Hypersensitive reaction may develop through a humoral or a cell mediated immune response.

2. Anaphylactic reactions initiated by antibody or antigen antibody complexes are referred to as **immediate hypersensitivity** because the symptoms are manifest within minutes or hours after a sensitized recipient encounters antigen.

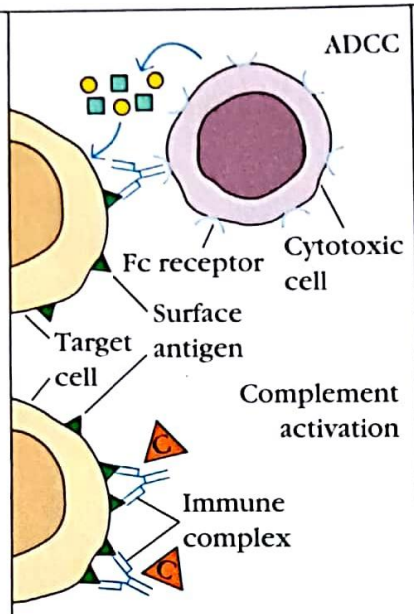
3. **Delayed-type hypersensitivity (DTH)** is named in recognition of the delay of symptoms until days after exposure.

4. Two immunologists, P. G. H. Gell and R. R. A. Coombs, proposed a classification scheme to discriminate among the various types of hypersensitivity. Hypersensitivities are classically divided into **four categories (types I–IV)** that differ by the immune molecules and cells that cause them, and the way they induce damage.

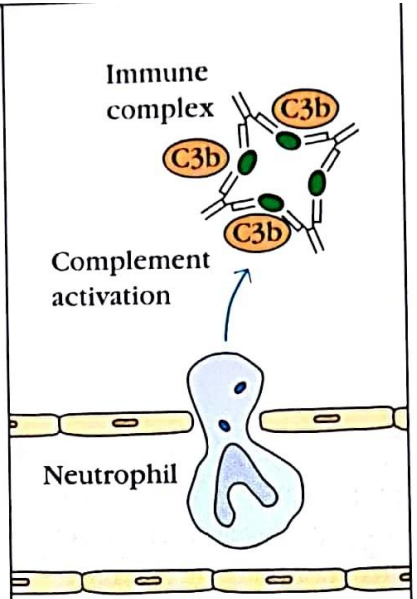
Four types of hypersensitive reactions



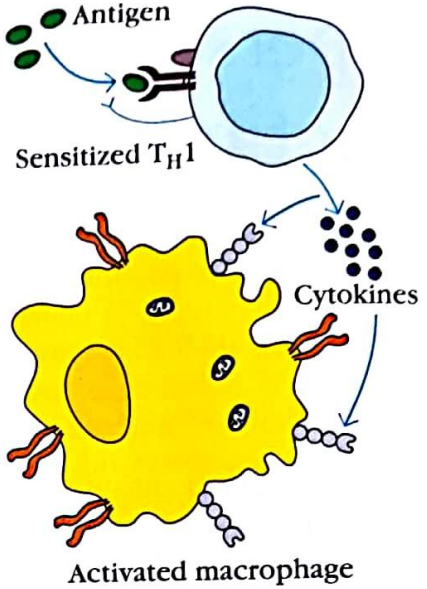
Type I



Type II

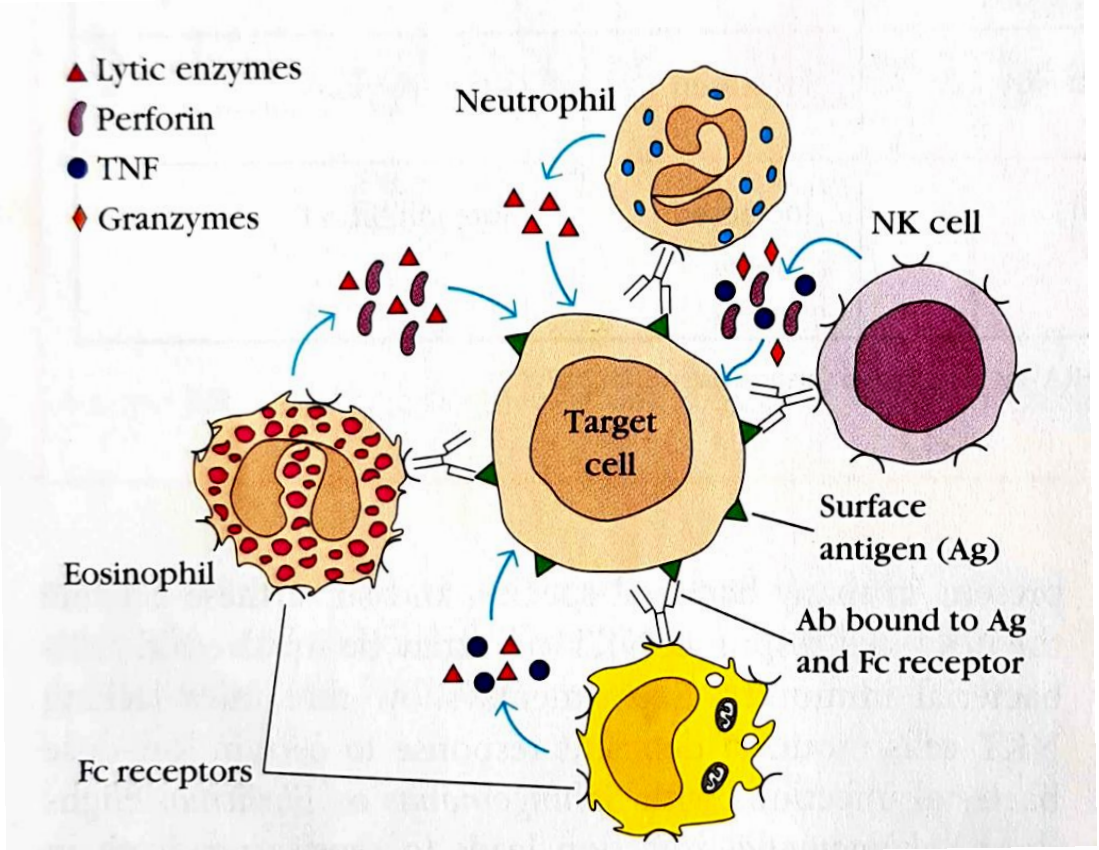


Type III



Type IV

IgE-Mediated Hypersensitivity	IgG- or IgM-Mediated Cytotoxic Hypersensitivity	Immune Complex–Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces cross-linking 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 shown above release cytokines that activate macrophages or T_C cells that mediate direct cellular damage. T_H2 cells and CTLs mediate similar responses.
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, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus.	Typical manifestations include contact dermatitis, tubercular lesions, and graft rejection.



Antibody-dependent cell-mediated cytotoxicity (ADCC). Nonspecific cytotoxic cells are directed to specific target cells by binding to the Fc region of antibody bound to surface antigens on the target cells. Various substances (e.g., lytic enzymes, TNF, perforin, granzymes) secreted by the nonspecific cytotoxic cells then mediate target-cell destruction.

IgE-Mediated (Type I) Hypersensitivity

1. This reaction is induced by a certain type of antigens referred to as allergens.
2. This is an example of allergen induced humoral antibody immune response.

3. Plasma cells secrete IgE in response to activation of allergen-specificT_H2 cells.

4. These antibodies bind with high affinity to Fc receptors on the surface of tissue mast cells and blood basophils. Both cells are sensitized. A later exposure to same allergen cross links the membrane bound antibodies and cause degranulation of these cells.

5. Pharmacologically active mediators released from the granules act on the surrounding tissue.

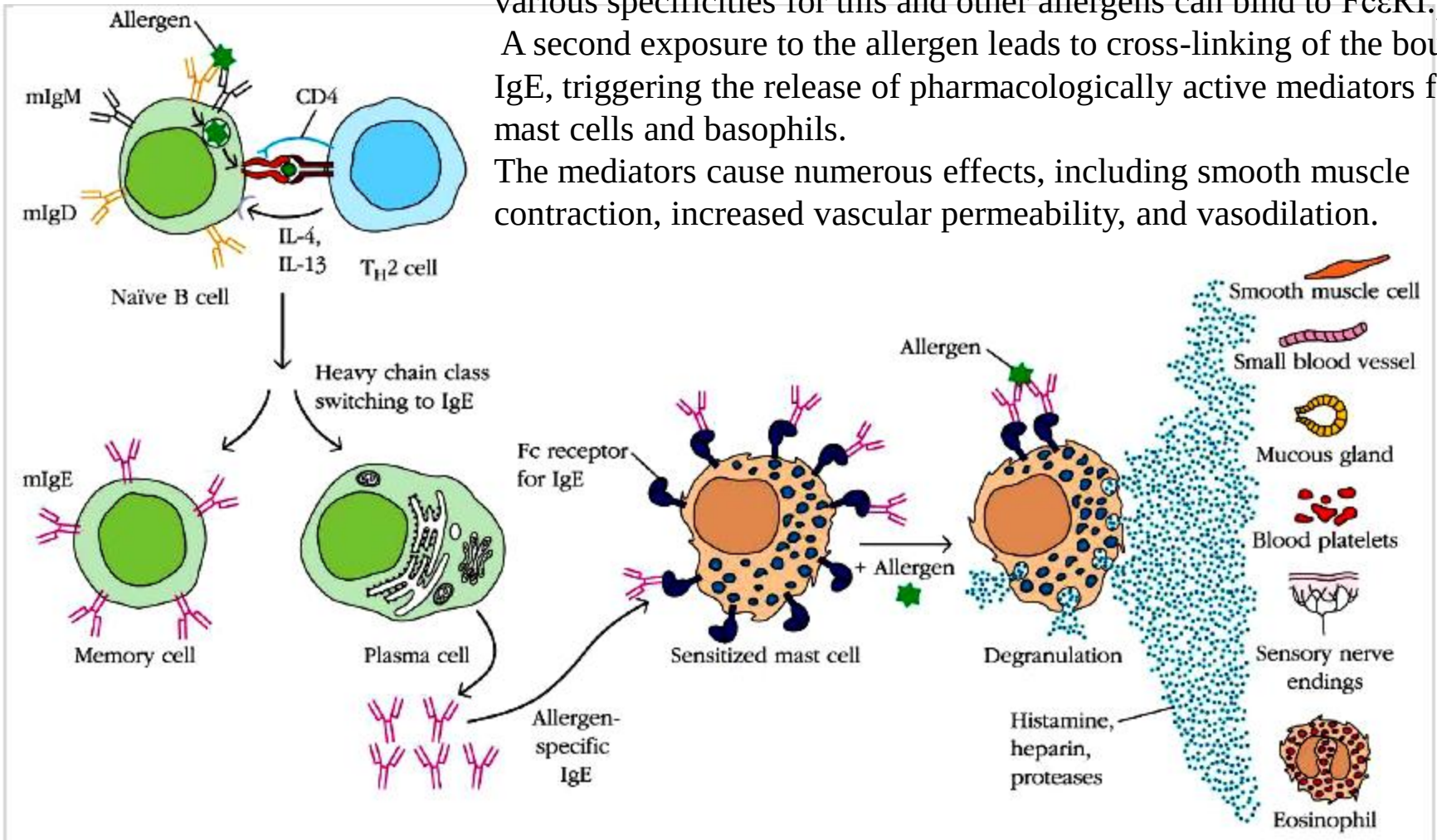
General mechanism underlying an immediate type I hypersensitivity reaction.

Exposure to an allergen activates T_H2 cells that stimulate B cells to proliferate, undergo heavy-chain class switching to IgE, and differentiate into IgE-secreting plasma cells and memory B cells expressing membrane IgE B-cell receptors (mIgE).

The secreted IgE molecules bind to IgE-specific Fc receptors (FcεRI) on mast cells and blood basophils. (Many molecules of IgE with various specificities for this and other allergens can bind to FcεRI.)

A second exposure to the allergen leads to cross-linking of the bound IgE, triggering the release of pharmacologically active mediators from mast cells and basophils.

The mediators cause numerous effects, including smooth muscle contraction, increased vascular permeability, and vasodilation.



Many allergens can elicit a Type I response

Individuals without allergies generate IgE antibodies only in response to parasitic infections. However, individuals who genetically are highly susceptible to allergies, a condition known as **atopy,** are predisposed to generate IgE antibodies against common environmental antigens. Chemical analyses revealed that most, if not all, allergens are highly soluble proteins or glycoproteins, usually with multiple epitopes, or antigenic determinants.

Common allergens associated with type I hypersensitivity

Plant pollens	**Drugs**
Rye grass	Penicillin
Ragweed	Sulfonamides
Timothy grass	Local anesthetics
Birch tree	Salicylates
Foods	**Insect products**
Nuts	Bee venom
Seafood	Wasp venom
Eggs	Ant venom
Peas, beans	Cockroach calyx
Milk	Dust mites
Other allergens	
Animal hair and dander	
Latex	
Mold spores	

A. First, many allergens have **intrinsic enzymatic activity** that contributes to the allergic response.

1. Allergens from dust mites (the allergenic component of house dust), cockroaches, pollen, fungi, and bacteria have **protease activity**. Some of these proteases have been shown to be capable of disrupting the integrity of epithelial cell junctions, allowing allergens to access the underlying cells and molecules of the innate and adaptive immune systems.

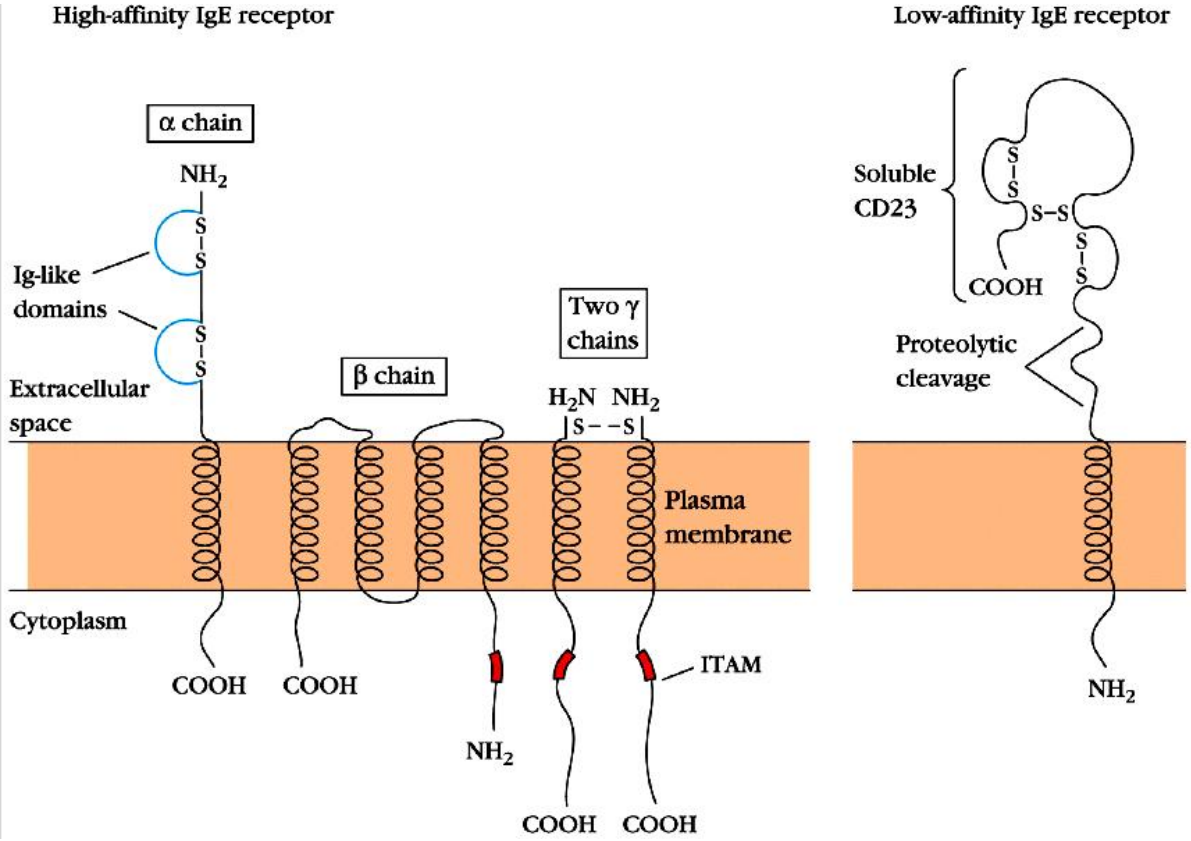
2. Others, including a protease (Der p 1) produced by the dust mite (*Dermatophagoides pteronyssinus*), **cleave and activate complement components** at the mucosal surface.

3. Still others **cleave and stimulate protease-activated receptors** on the surfaces of immune cells, enhancing inflammation. Several cleave the inactive form of the IL-33 cytokine produced by epithelial cells, generating active IL-33 that contributes to allergic responses.

One factor that distinguishes allergenic from nonallergenic antigens may be the presence of protease activity that affects the cells and molecules of the immune system.

B. Second, many allergens contain potential pathogen-associated molecular patterns, or PAMPS capable of interacting with receptors of the innate immune system and initiating a cascade of responses that contribute to an allergic response.

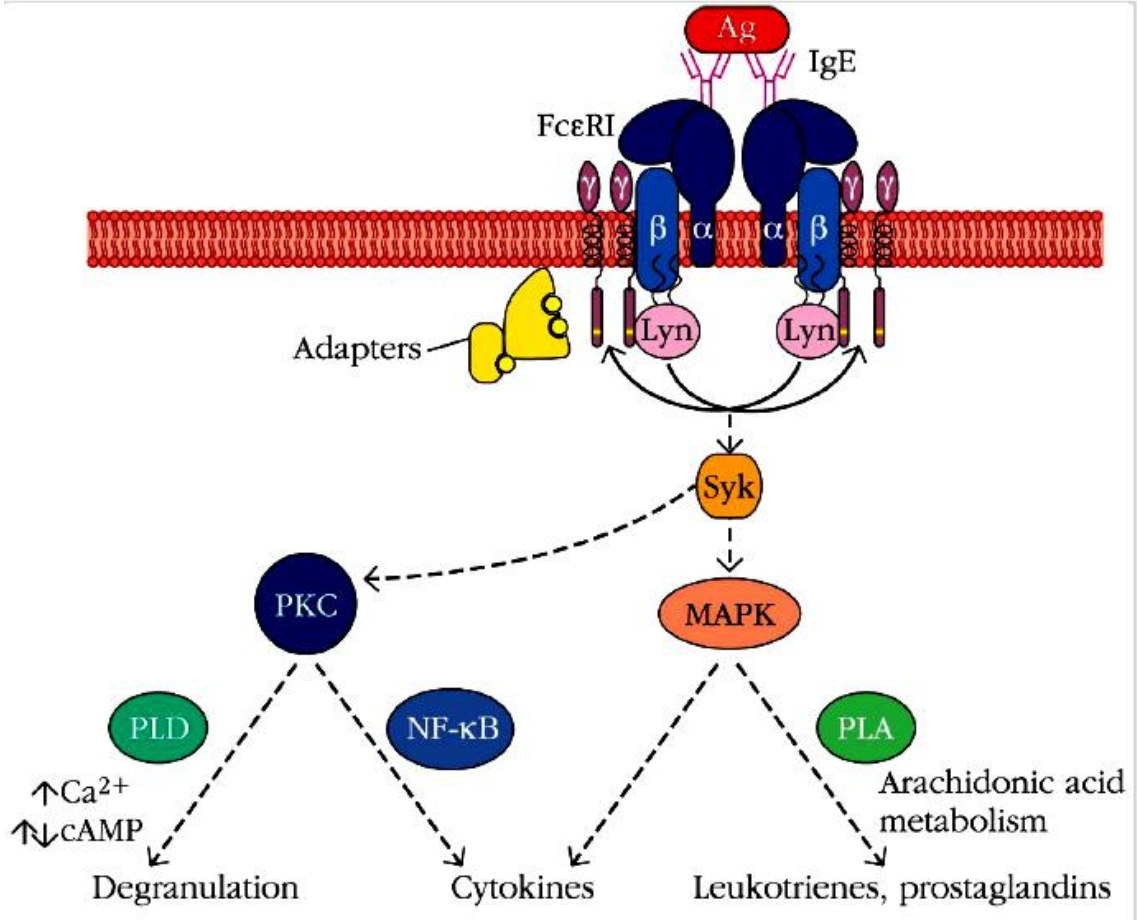
C. Third, many allergens enter the host via mucosal tissues at very low concentrations, which tend to induce T_H 2 responses. The IL-4 and IL-13 produced by T_H 2 cells induce heavy-chain class switching to IgE during the generation both of plasma cells secreting allergen-specific antibodies and of allergen-specific memory B cells



Schematic diagrams of the high-affinity FcεRI and low-affinity FcεRII receptors that bind the Fc region of IgE.

(a) FcεRI consists of an α chain that binds IgE, a β chain that participates in signaling, and two disulfide-linked γ chains that are the most important component in signal transduction. The β and γ chains contain cytoplasmic ITAMs, a motif also present in the Igα/Igβ (CD79α/β) heterodimer of the B-cell receptor and in the CD3 chains of the T-cell receptor complex.

(b) The single-chain FcεRII is unusual because it is a type II transmembrane protein, oriented in the membrane with its NH terminus directed toward the cell interior and its COOH terminus directed toward the extracellular space.

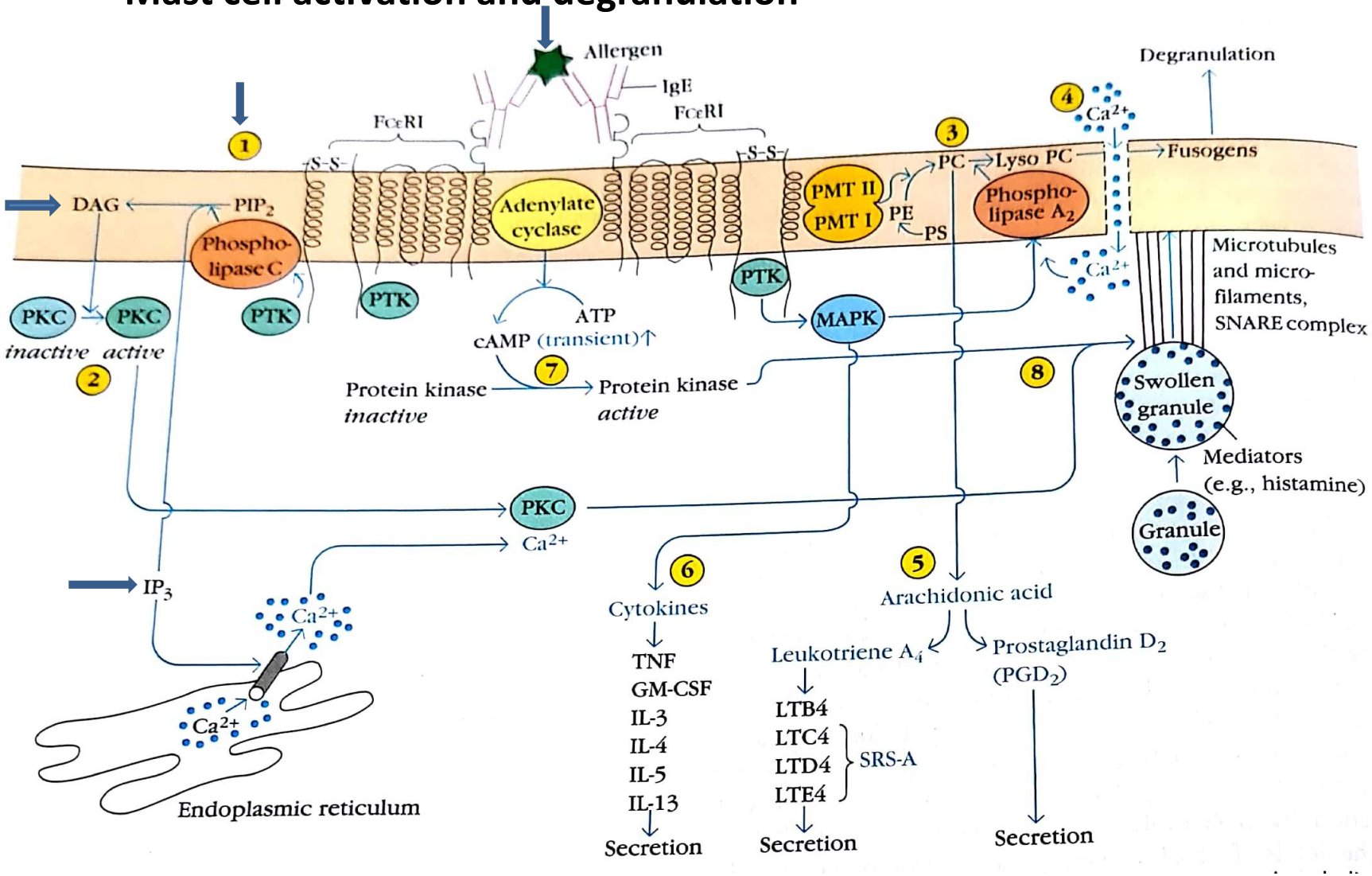


Signaling pathways initiated by IgE allergen cross-linking of FcεRI receptors.

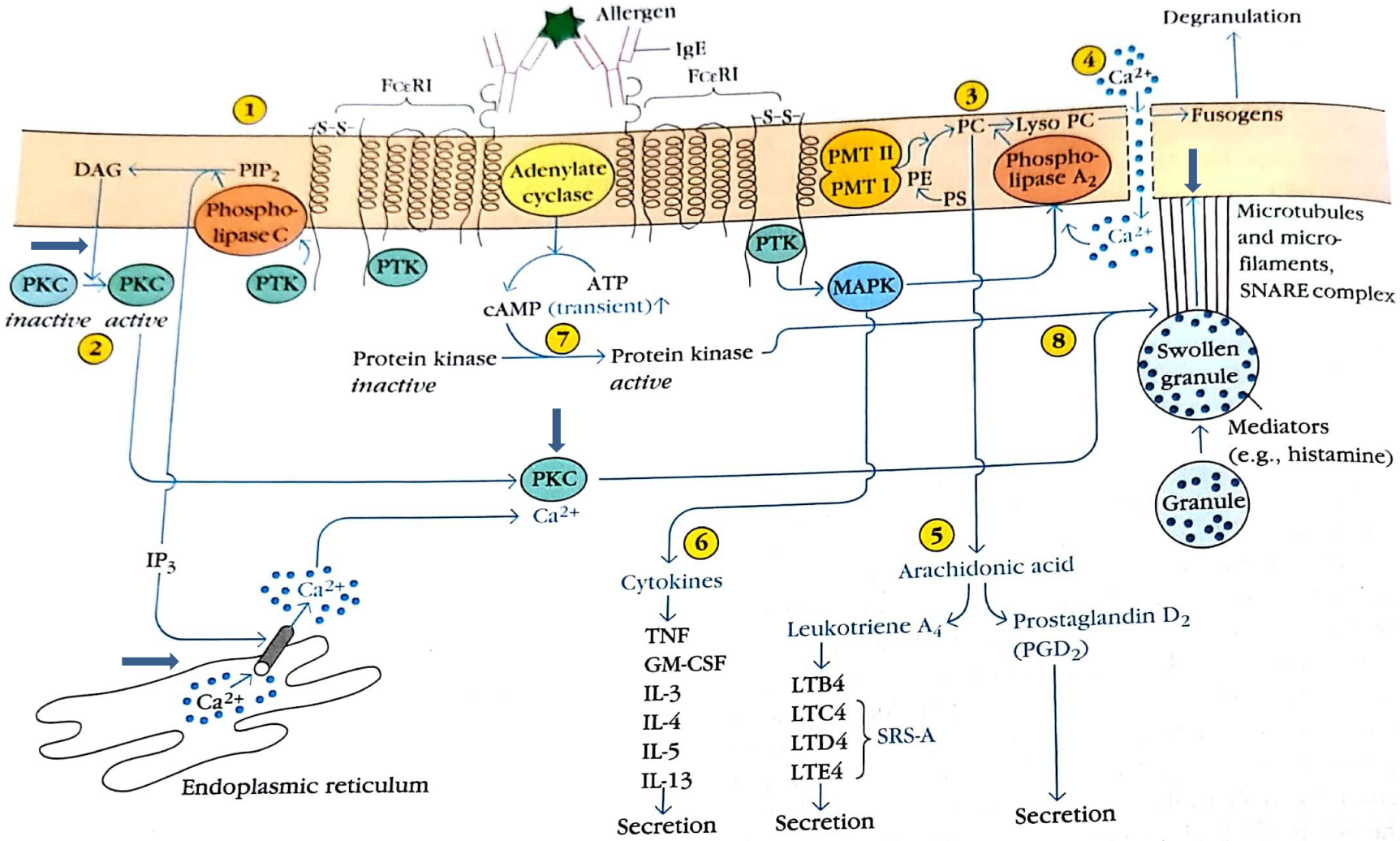
By cross-linking FcεRI receptors, IgE initiates signals that lead to mast cell degranulation and release of prepackaged mediators, cytokine production, and leukotriene and prostaglandin generation.
The signaling cascades initiated by the FcεRI are generally similar to those initiated by antigen receptors.

Cross-linking of FcεRI activates the tyrosine kinase Lyn, which phosphorylates the receptor ITAMs and activates the tyrosine kinase Syk, which phosphorylates adapter molecules that organize signaling responses.
Multiple kinases are activated, including protein kinase C (PKC) and various mitogen-activated protein kinases (MAPKs). These, in turn, activate transcription factors (e.g., NF-κB) that regulate cytokine production. They also activate lipases, including phospholipase D (PLD), and stimulate an increase in intracellular free calcium ions and a transient increase in cAMP all of which induce degranulation.
Phospholipase A (PLA) is activated, initiating the production of leukotrienes and prostaglandins from the metabolism of arachidonic acid.

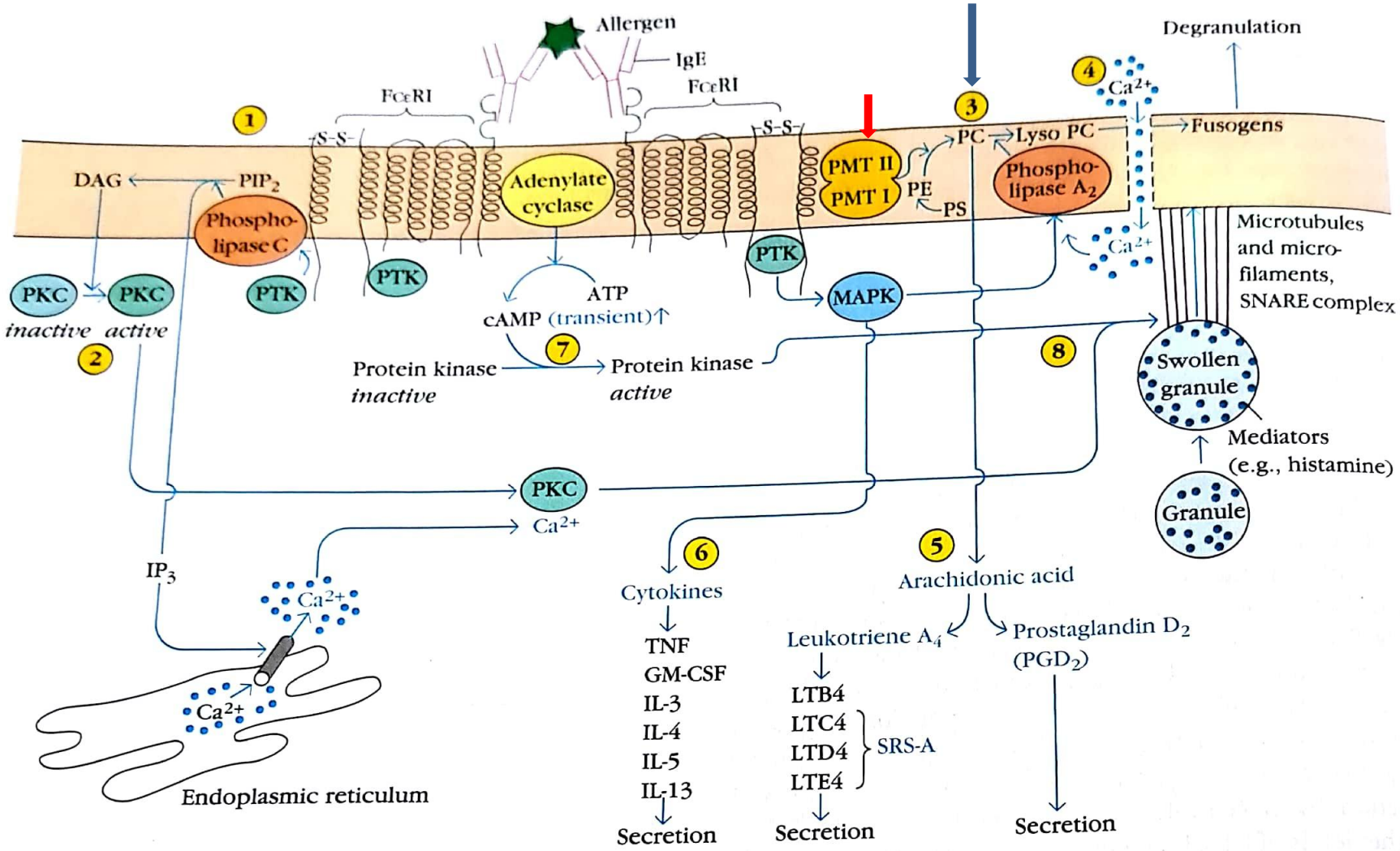
Mast cell activation and degranulation



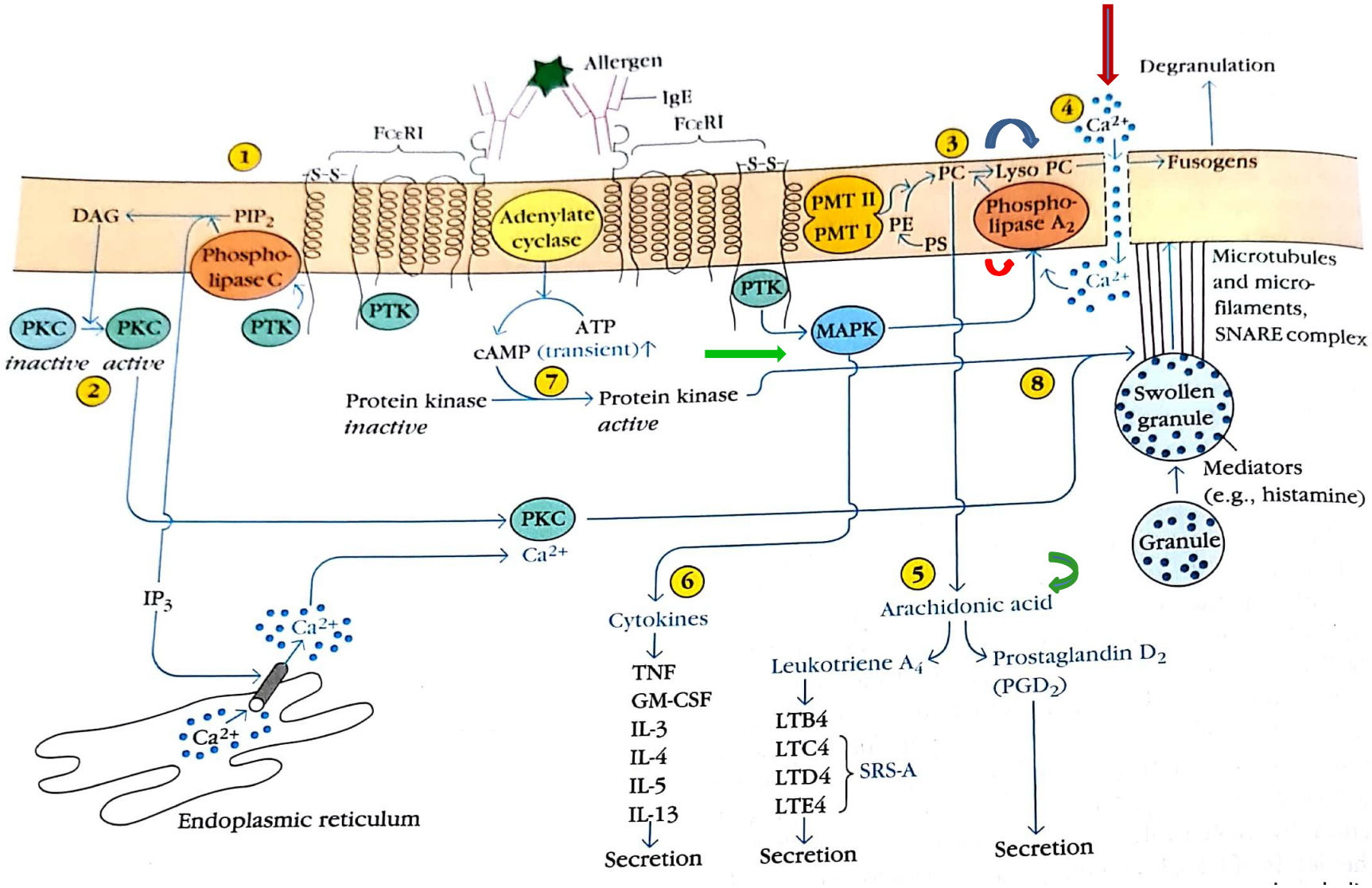
1. Activation of protein Tyrosine Kinase (PTK)
2. PTK phosphorylates phospholipase C which converts phosphatydillinositol-4,5 bisphosphate (PIP2) into diacylglycerol (DAG) and inositol triphosphate(Ip3)



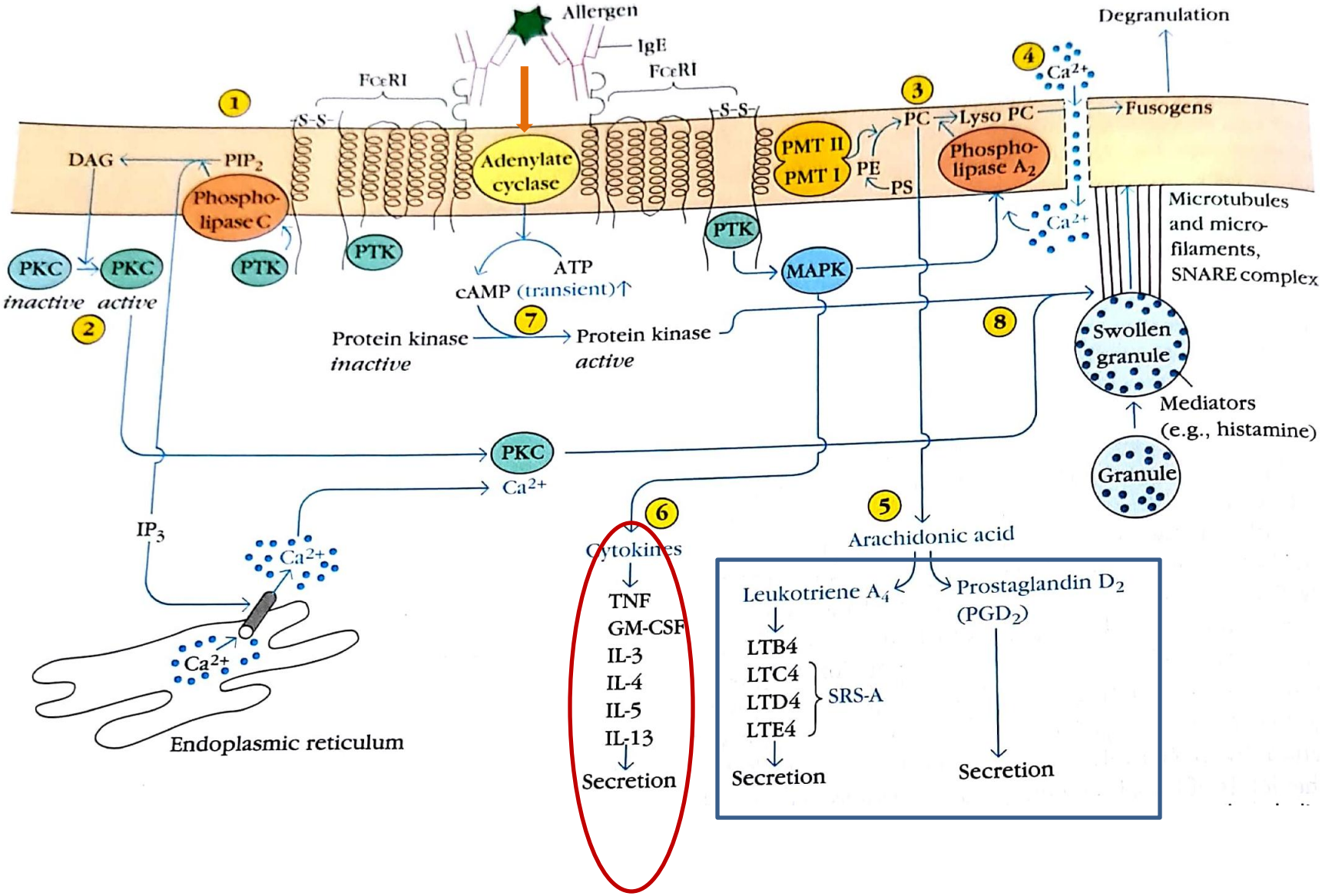
2. DAG activated protein kinase C (PKC), which with Ca^{2+} is necessary for microtubuler assembly and the fusion of the granules with the plasma membrane. IP3 is a potent mobilizer of intracellular Ca^{2+}stores.



3. Crosss linkage of FcεR1 also activates an enzyme that converts phosphatidylserine (PS) into phosphatidylethanolamine (PE). PE is methylated toform phosphatidylcholine (PC) by the phospholipid methyl transferase enzymes I and II (PMT I and II).



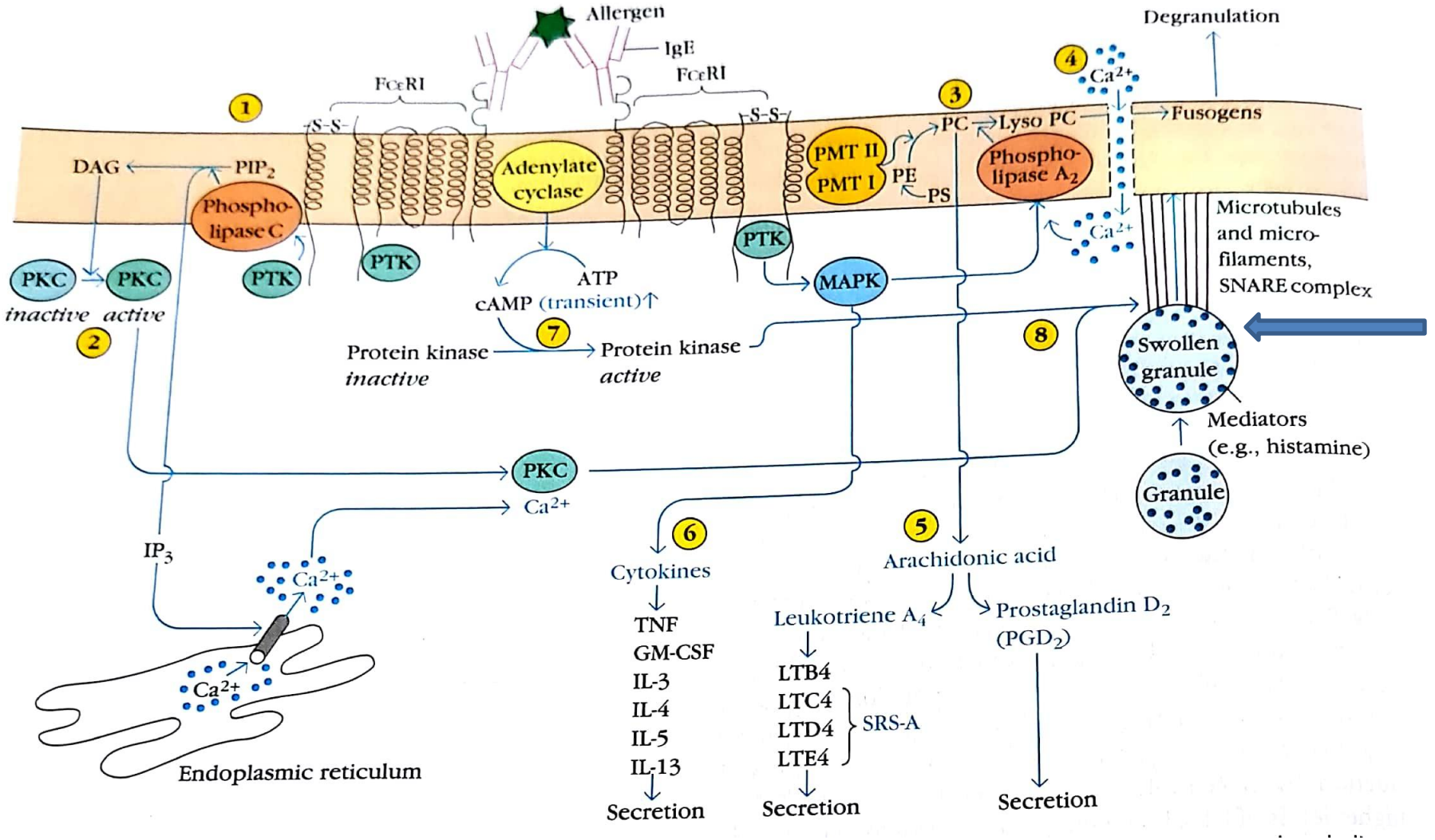
4. Accumulation of PC on the exterior surface of the plasma membrane causes an increase in membrane fluidity and facilitates the formation of Ca^{2+} channels. Influx of calcium and PTK-activated mitogen-activated protein kinase (MAPK) activates phospholipase A_2 which promoted break dowm of PC into lysophosphatidylcholine Lyso PC and arachidonic acid.



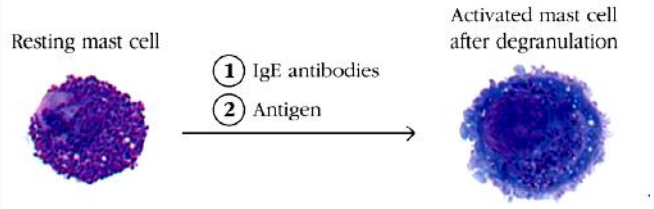
5. Arachidonic acid is converted into potent lipid mediators: Prostaglandins and leukotrienes(slow reactive substance of anaphylaxix, SRS-A).

6. Activated MAPK induces secretion of cytokines by increasing transcription of cytokine genes.

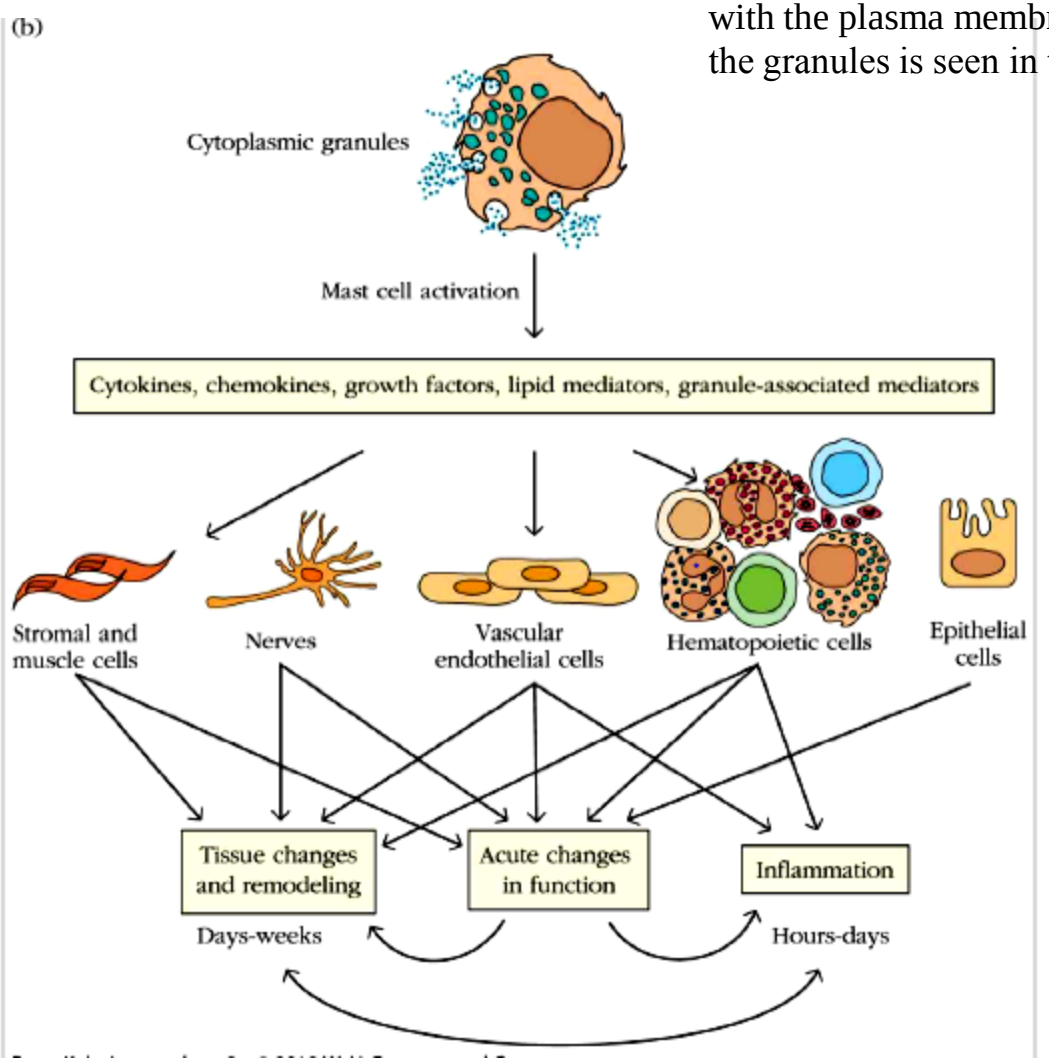
7. Cross linkage of membrane receptors activates membrane Adenylate cyclase leading to transient increase of cAMP-dependent protein kinase required for degranulation.



8. Granule membrane proteins are phosphorylated by C-AMP dependent protein kinase therby changing permeability of granules to water and Ca2+. Subsequent swelling and formation of soluble N-ethymaleimide attachment receptor (**SNARE)** protein complex which facilitates fusion with the plasma membrane and release of the mediators.



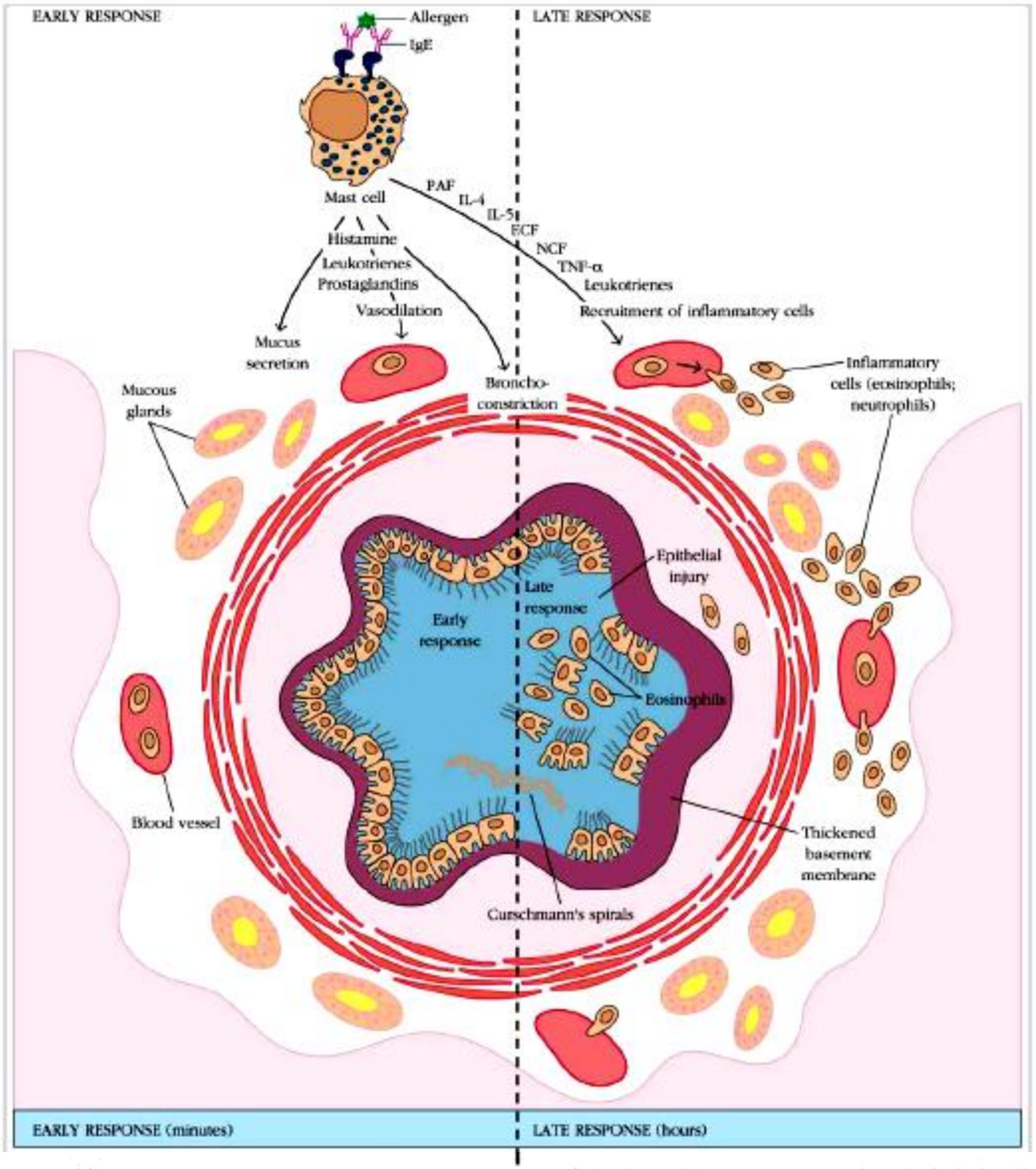
Effects of mast cell activation.
(a) Mast cells before (left) and after degranulation (right) induced by IgE antibodies and antigen that is bound by the antibodies. Resting mast cells have numerous granules (secretory vesicles) stored in their cytoplasm. After the mast cell is activated by addition of IgE antibodies (which bind to FcεRI) and an antigen that cross-links the IgE antibodies, the granules fuse with the plasma membrane, releasing their contents. Extra membrane from the granules is seen in the cell's plasma membrane after degranulation.



(b) Mast cell mediators and their effects. Various stimuli activate mast cells to secrete different types and/or amounts of products. Activated mast cells immediately release preformed, granule-associated inflammatory mediators (including histamine, proteases, and heparin) and are induced to generate lipid mediators (such as leukotrienes and prostaglandins), chemokines, cytokines, and growth factors (some of which can also be packaged in granules). These mediators act on different cell types, and have both acute and chronic effects. When produced over long periods of time, mast cell mediators have a significant influence on tissue structure by enhancing proliferation of fibroblasts and epithelial cells, increasing production and deposition of collagen and other connective tissue proteins, stimulating the generation of blood vessels, and more.

Principal mediators involved in type I hypersensitivity

Mediator	Effects
	Primary
Histamine, heparin	Increased vascular permeability; smooth muscle contraction
Serotonin (rodents)	Increased vascular permeability; smooth muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A)	Neutrophil chemotaxis
Proteases (tryptase, chymase)	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 adhesion molecules on venous endothelial cells
IL-4 and IL-13	Induction of T_H2 cells, increased IgE production
IL-3, IL-5, IL-6, IL-8, IL-9, IL-10, TGF-β, and GM-CSF	Various effects (see text)



Histamine	Vasodilation	IL-4, TNF-α, LTC_4	Increased endothelial cell adhesion
Prostaglandins	Bronchoconstriction	PAF, IL-5, ECF	Leukocyte migration
Leukotrienes	Mucus secretion	IL-4, IL-5	Leukocyte activation

The early and late inflammatory responses in asthma.

Early responses mediated by IgE binding to mast cells, triggering degranulation and mediator release, occur within about 30 minutes of allergen inhalation, while late responses may take 6 to 12 hours.

The effects of various mediators on an airway, represented in cross-section, are illustrated in the center.

Chronic asthma can result in more serious effects, including disruption of the epithelial barrier, thickening of the basement membrane and smooth muscle layer, and increase in mucus-secreting cells.

Localized Hypersensitivity Reactions

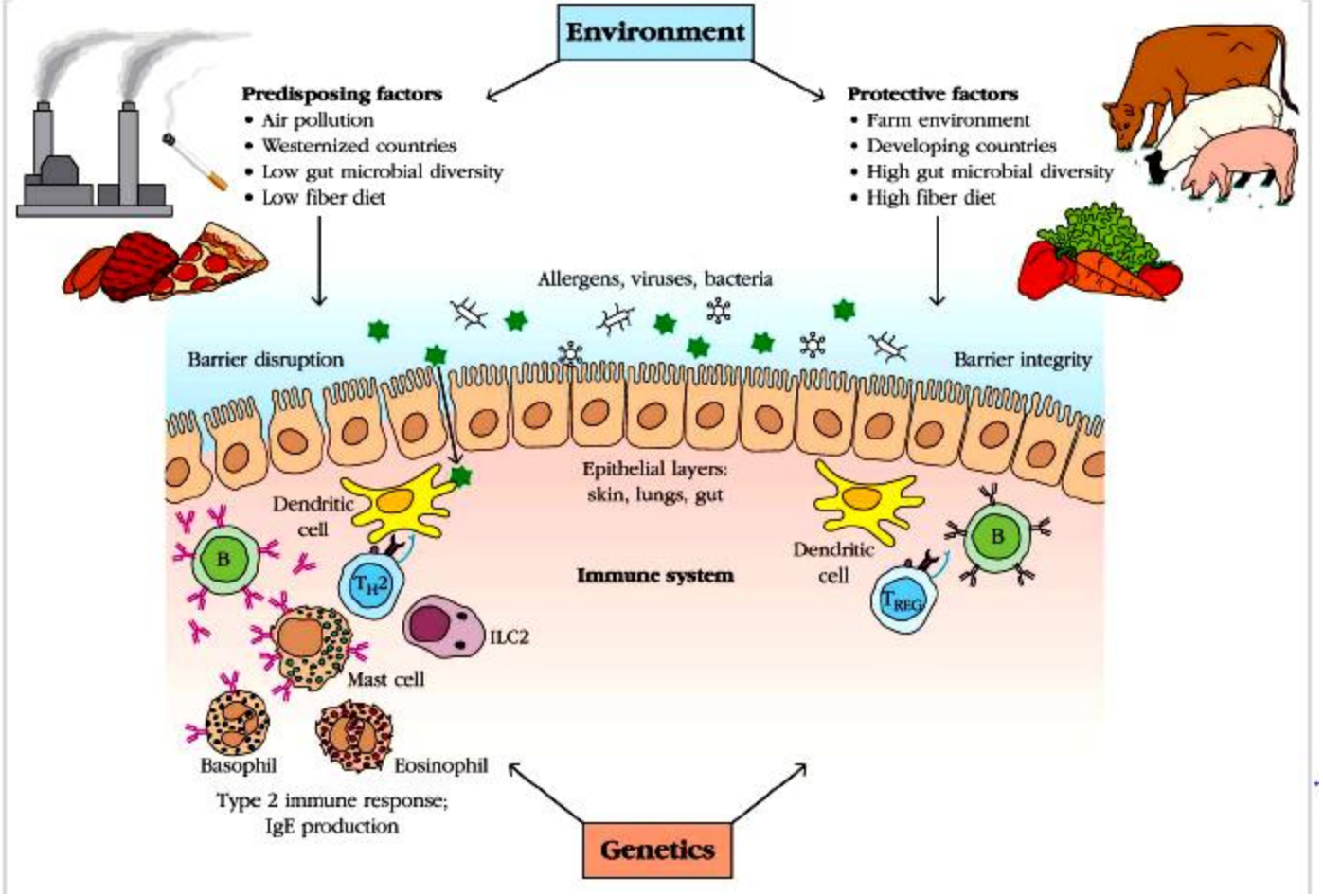
In localized hypersensitivity reactions, the effects are limited to a specific target site in a tissue or organ, often occurring at the epithelial surfaces first exposed to allergens. These localized allergic reactions include a wide range of IgE-mediated reactions: allergic rhinitis (hay fever), asthma, atopic dermatitis (eczema), urticaria (hives), angioedema (deep tissue swelling), and food allergies. The most common localized hypersensitivity reaction is allergic rhinitis or hay fever.

Symptoms result from the inhalation of common airborne allergens (pollens, dust, animal dander, mold spores),

Systemic Anaphylaxis

The most severe type of allergic response, **anaphylaxis, is a systemic, often fatal state that occurs** within minutes of exposure to an allergen. It is usually initiated by an allergen introduced directly into the bloodstream or absorbed into the circulation from the gut or skin. Symptoms include a precipitous drop in blood pressure leading to anaphylactic shock, followed by contraction of smooth muscles leading to defecation, urination, and bronchiolar constriction causing labored respiration. This can lead to asphyxiation, which can cause death within 2 to 4 minutes of exposure to the allergen. These symptoms are all due to rapid and widespread IgE antibody-mediated degranulation of mast cells and basophils and the systemic effects of their contents.

A wide range of allergens has been shown to trigger this reaction in susceptible humans, including the venom from bee, wasp, hornet, and ant stings; drugs such as penicillin, insulin, and antitoxins; foods such as seafood and nuts; and latex. If not treated quickly, these reactions can be fatal.

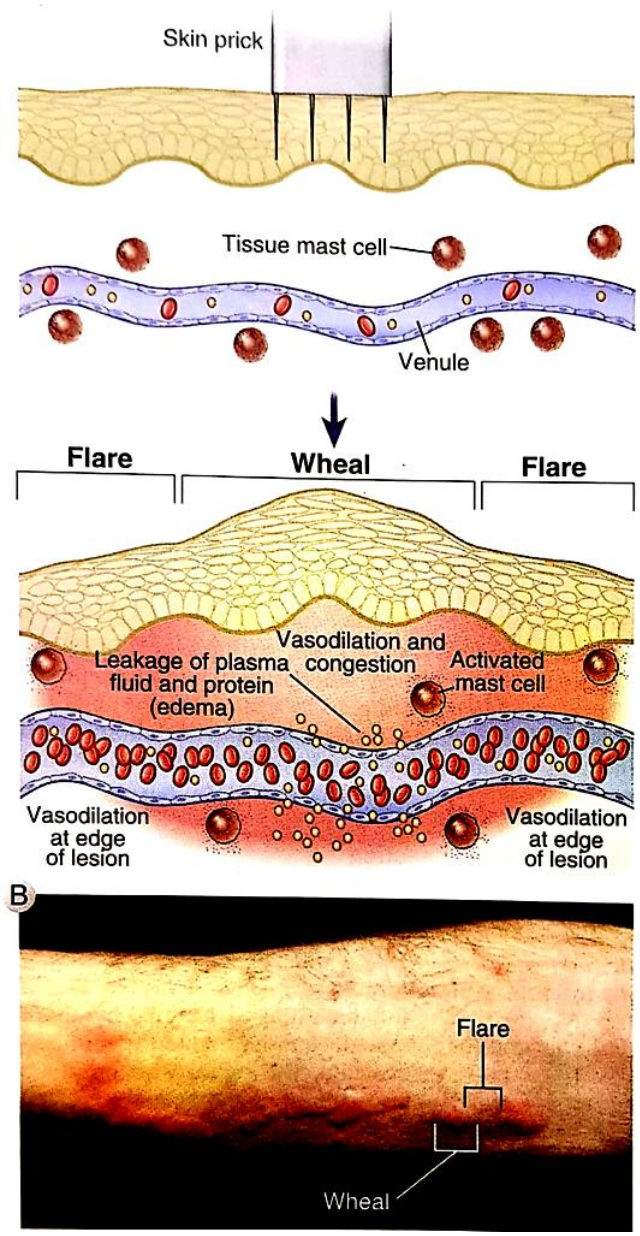


Environmental factors and genetics influence predisposition to allergies. Exposure to environments with significant microbial content, such as those including farm animals, and diets high in fiber are protective. In contrast, environmental factors that enhance development of type I hypersensitivities include air pollution (such as smoke from trucks and factories, second-hand cigarette smoke, and ozone typical of Western industrialized countries), low fiber diet, and low microbial exposure (e.g., in areas with good sanitation and use of vaccines and antibiotics). These factors contribute to the disruption of the integrity of epithelial barrier layers. Genetic differences also influence the mucosal immune system. Development of type 2 immunity, involving dendritic cells, ILC2 cells, and T 2 cells—which all promote IgE antibody production—leads to H allergic responses.

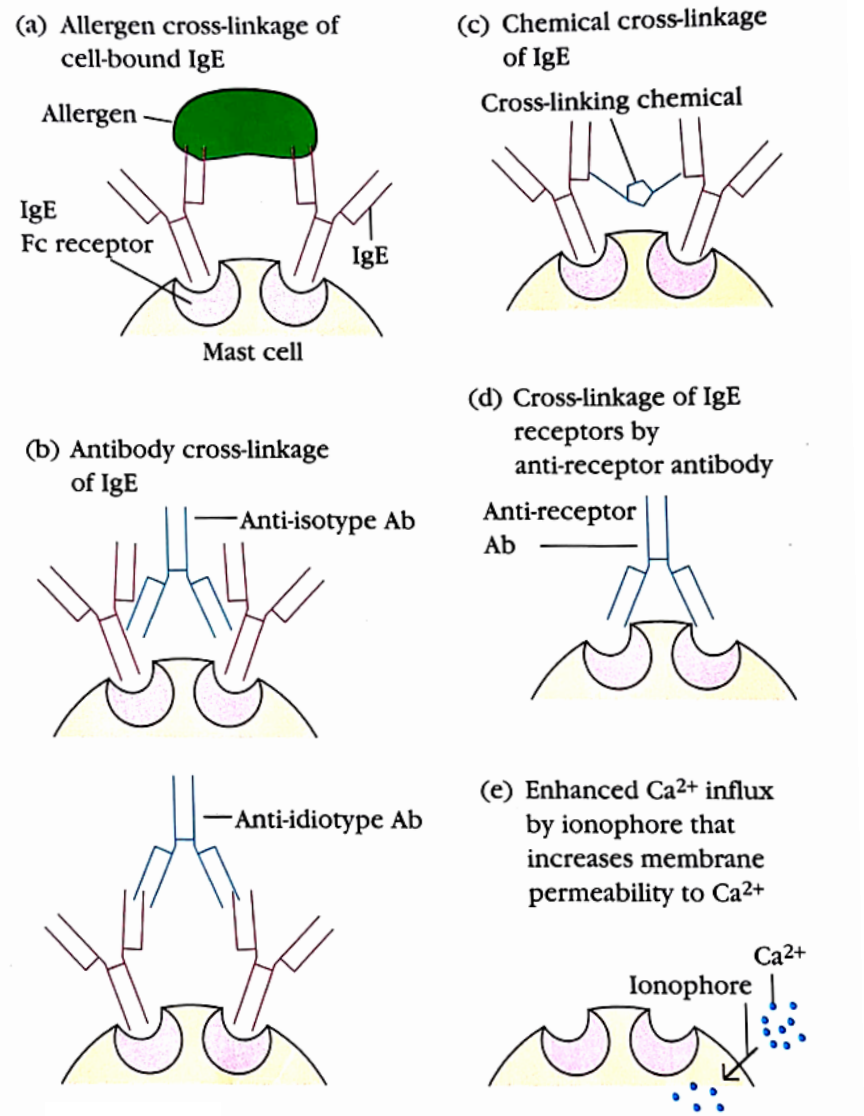
The hygiene hypothesis

The early findings that susceptibility to type I hypersensitivity conditions is high in Western industrialized societies and reduced in environments where there is early exposure to microbes, as is found in many developing countries, led to the **hygiene hypothesis.**

This hypothesis proposes that exposure to some pathogens during infancy and childhood benefits individuals by stimulating immune responses other than the type 2 responses that induce IgE responses and allergies.



The wheal and flare reaction in the skin and allergy skin test



Schematic diagrams of mechanisms that can initiate 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 cross-linkage.

Allergens not always required for type I hypersensitive reaction

Majority of humans mount significant IgE responses only as a defense against parasitic infections. Level of serum IgE remains high until the parasite is successfully cleared from the body.

Some people may have abnormality where they produce IgE in response to common environmental antigens. It is a hereditary predisposition to develop immediate hyper sensitivity and such abnormality is called **atopy**.

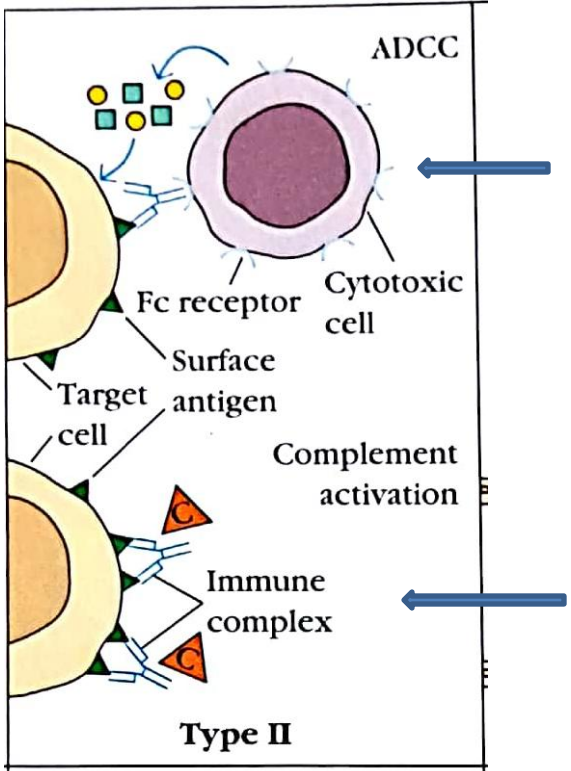
Antibody-Mediated (Type II) Hypersensitivity

Type II hypersensitivity reactions involve antibody-mediated destruction of cells by IgG and IgM immunoglobulins. Antibody bound to a cell-surface antigen can induce death of the antibody bound cell by three distinct mechanisms.

First, certain immunoglobulin subclasses can activate the complement system, creating pores in the membrane of a foreign cell.

Second, antibodies can mediate cell destruction by antibody-dependent cell-mediated cytotoxicity (ADCC), in which cytotoxic cells bearing Fc receptors bind to the Fc region of antibodies on target cells and promote killing of the cells.

Third, antibody bound to a foreign cell also can serve as an opsonin, enabling phagocytic cells with Fc receptors or (after complement has been activated by the bound antibodies) receptors for complement fragments such as C3b to bind and phagocytose the antibody-coated cell.

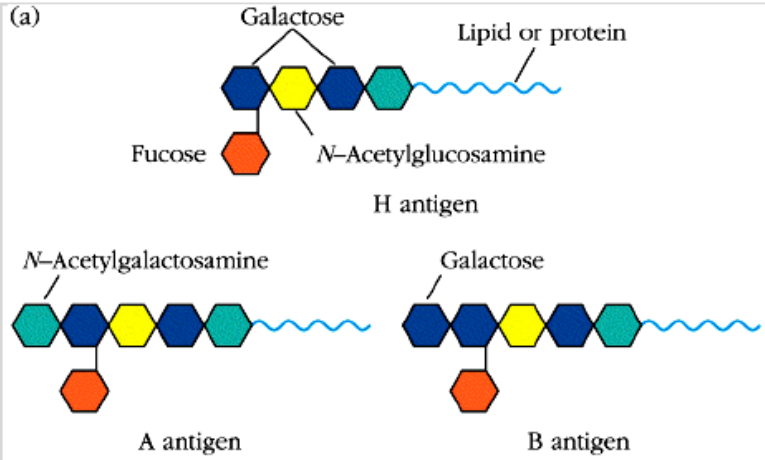


IgG- or IgM-Mediated Cytotoxic Hypersensitivity

Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC.

Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia.

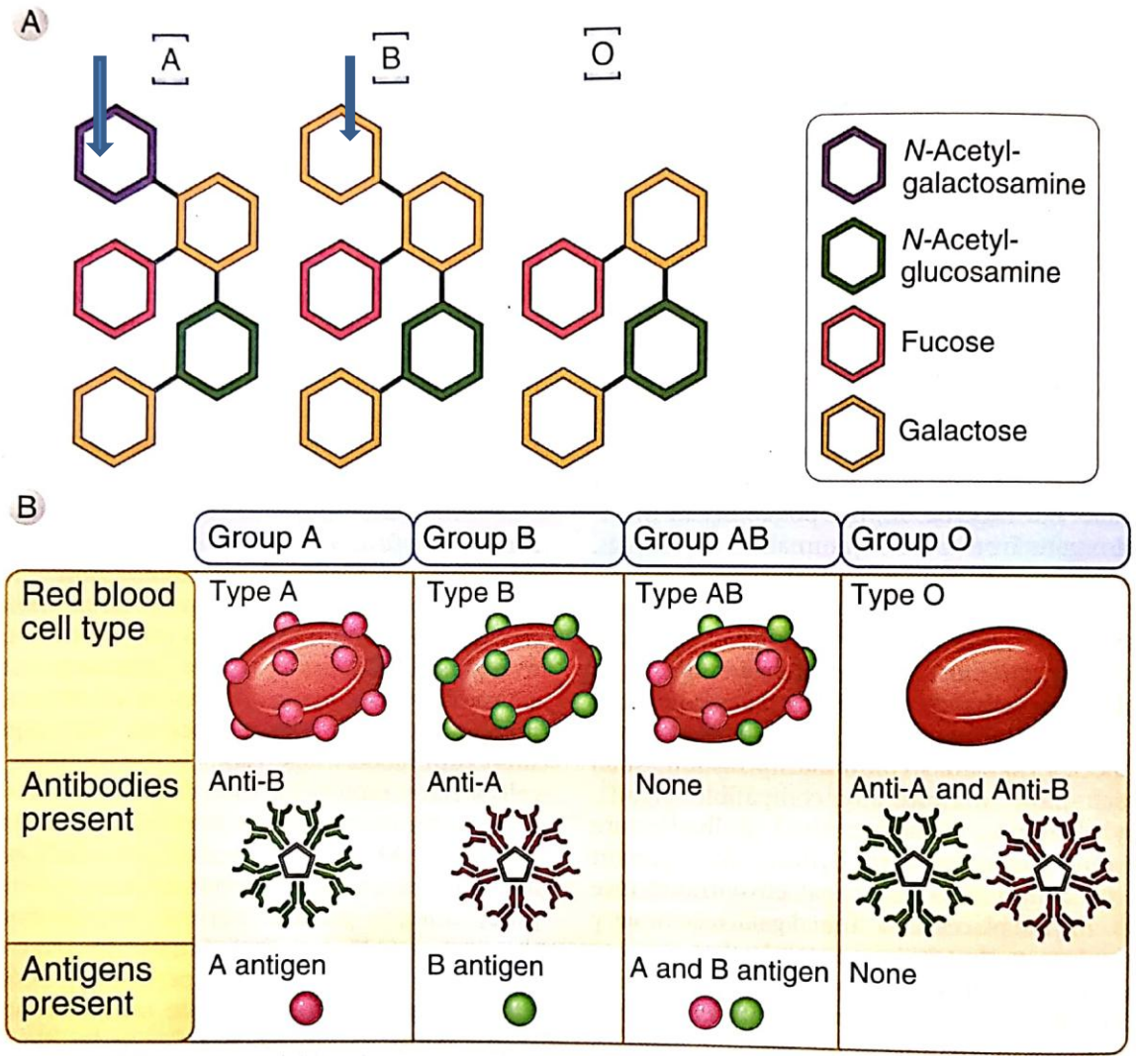
Transfusion reactions are type II reactions:
If a type A individual is transfused with blood containing type B cells, a transfusion reaction occurs in which the anti –B isohemagglutinins bind to B blood cells and mediate their destruction by means of complement mediated lysis.
Massive intra vascular hemolysis of transfused red blood cells takes place. Free hemoglobin is detected in plasma. Antibodies to other blood group antigens may result from repeated blood transfusion because minor allelic differences in these antigens can stimulate antibody production.



(b)

Genotype	Blood–group phenotype	Antigens on erythrocytes *(agglutinins)*	Serum antibodies *(isohemagglutinins)*
AA or AO	A	A	Anti–B
BB or BO	B	B	Anti–A
AB	AB	A and B	None
OO	O	H	Anti–A and anti–B

ABO (ABH) blood groups. (a) Structure of terminal sugars, which constitute the distinguishing epitopes of the A, B, and H blood antigens. All individuals express the H antigen, but not all individuals express the A or B antigens. The blood group of those who express neither A or B antigens (but, like all people express the H antigen) is referred to as O. (b) ABO genotypes, corresponding phenotypes, agglutinins (antigens), and isohemagglutinins (antibodies that react to nonhost antigens).



The ABO antigens are carbohydrates, linked to cell surface lipids and proteins. These are synthesized by polymorphic glycosyltransferase enzymes that vary in activity depending on the inherited allele.

Most individuals possess a fucosyltransferase that adds a fucose moiety to the nonterminal sugar residue of the core **glycan.** The fucosylated glycan is called **the H antigen.**

Different blood groups are produced by addition of different sugars by different inherited glycosyltransferases.

The **O allele** gene product is devoid of any enzyme activity.

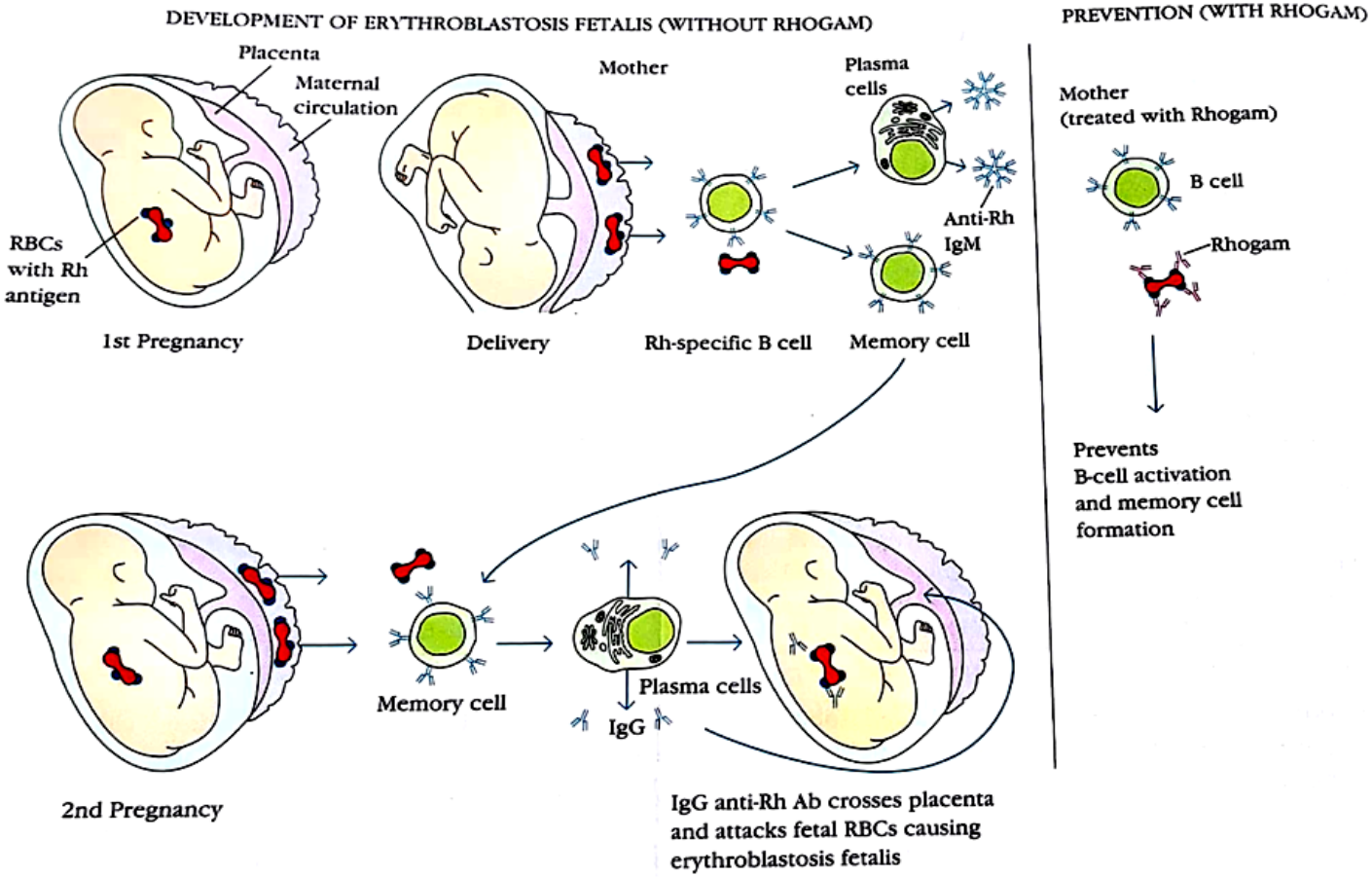
The A allele encoded enzyme transfers a terminal N-acetylgalactosamine moity onto the H antigen

The B allele gene product transfers a terminal galactose moiety.

Transfusion reactions are type II reactions:
If a type A individual is transfused with blood containing type B cells, a transfusion reaction occurs in which the anti –B isohemagglutinins bind to B blood cells and mediate their destruction by means of complement mediated lysis.
Massive intra vascular hemolysis of transfused red blood cells takes place. Free hemoglobin is detected in plasma. Antibodies to other blood group antigens may result from repeated blood transfusion because minor allelic differences in these antigens can stimulate antibody production.

An Rh mother pregnant by an Rh father is in danger of developing a response to the Rh antigen that the fetus may have inherited from the father and rejecting the Rh fetus. 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. However, at the time of delivery, separation of the placenta from the uterine wall allows larger amounts of fetal umbilical cord blood to enter the mother's circulation. These fetal red blood cells stimulate Rhspecific B cells to mount an immune response, resulting in the 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 memory cells remain, a threat to any subsequent pregnancy with an Rh fetus. Importantly, since IgM antibodies do not pass through the placenta, IgM anti-Rh antigens are no threat to the fetus.

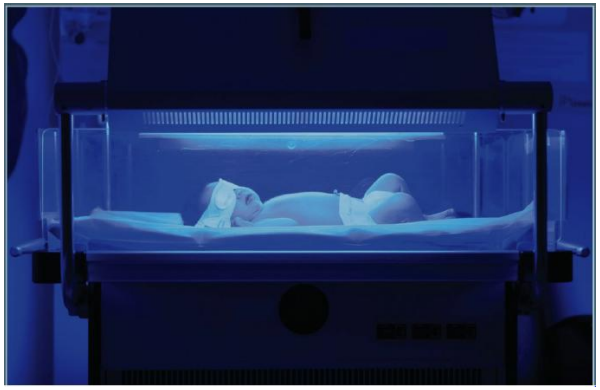
However, activation of IgG-expressing memory cells in a subsequent pregnancy results in the formation of IgG anti-Rh antibodies, which can cross the placenta and damage the fetal red blood Cells.



Development of erythroblastosis fetalis (hemolytic disease of the newborn) caused when an Rh^- mother carries an Rh^+ fetus *(left)* and effect of treatment with anti-Rh antibody, or Rhogam *(right)*.

Hemolytic disease of the newborn caused by Rh incompatibility in a second or later pregnancy can be almost entirely prevented by administering antibodies against the Rh antigen to the mother at around 28 weeks of her first pregnancy and within 24 to 48 hours after the first delivery. Anti-Rh antibodies are also administered to pregnant women after amniocentesis. These antibodies, marketed as RhoGAM, bind to any fetal red blood cells that may have entered the mother's circulation 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 cross the placenta.



Ultraviolet light is used to treat bilirubinemia of the newborn.

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. Because the blood-brain barrier is not complete until after birth, very young babies can suffer fatal brain damage from bilirubin. Fortunately, bilirubin is rapidly broken down on exposure of the skin to ultraviolet (UV) light, and babies who display the telltale jaundiced appearance that signifies high levels of blood bilirubin are treated by exposure to UV light in their cribs

Hemolytic anemia can be drug induced

Certain antibiotics (e.g., penicillin, cephalosporins, and streptomycin), as well as other well known drugs (including ibuprofen and naproxen), can adsorb nonspecifically to proteins on red blood cell membranes, forming a drug-protein complex. In some patients, such drug-protein complexes induce the formation of antibodies. These antibodies then bind to the adsorbed drug on red blood cells, inducing complement-mediated lysis and thus progressive anemia. When the drug is withdrawn, the hemolytic anemia disappears. Penicillin is notable in that it can induce all four types of hypersensitivity with various clinical manifestations.

Penicillin-induced hypersensitivity reactions

Type of reaction	Antibody or lymphocyte induced	Clinical manifestations
I	IgE	Urticaria, systemic anaphylaxis
II	IgM, IgG	Hemolytic anemia
III	IgG	Serum sickness, glomerulonephritis
IV	T cells	Contact dermatitis

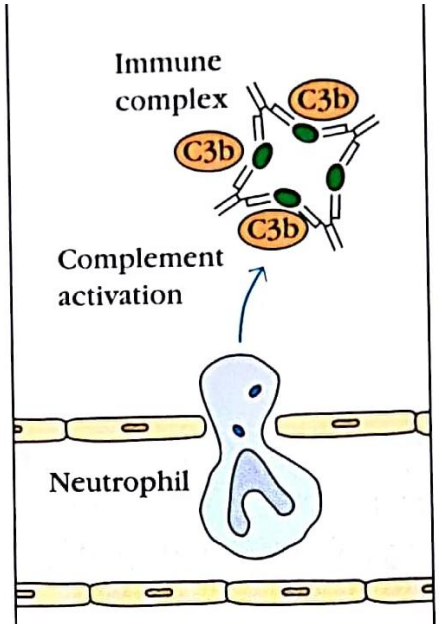
Immune Complex–Mediated (Type III) Hypersensitivity

The reaction of antibody with antigen generates immune complexes. In general, these antigenantibody complexes facilitate the clearance of antigen by phagocytic cells and red blood cells. In some cases, however, the presence of large numbers and networks of immune complexes can lead to tissue-damaging type III hypersensitivity reactions.

The magnitude of the reaction depends on the levels and size of immune complexes, their distribution within the body, and the ability of the phagocyte system to clear the complexes and thus minimize the tissue damage.

Failure to clear immune complexes may also result from peculiarities of the antigen itself, or disorders in phagocytic machinery. The deposition of immune complexes in the blood vessels or tissues initiates reactions that result in the recruitment of complement components and neutrophils to the site, with resultant tissue injury.

The conditions which induce type III hyper sensitive response include
(1) the presence of antigens capable of generating particularly extensive antigen-antibody lattices,
(2) a high intrinsic affinity of antigens for particular tissues,
(3) the presence of highly charged antigens (which can affect immune complex engulfment), and
(4) a compromised phagocytic system.



Type III

Immune Complex-Mediated Hypersensitivity
Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils.
Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus.

Uncleared immune complexes bind to mast cells, neutrophils, and macrophages via Fc receptors, triggering the release of vasoactive mediators and inflammatory cytokines, which interact with the capillary epithelium and increase the permeability of the blood vessel walls.

Immune complexes then move through the capillary walls and into the tissues, where they are deposited and set up a localized inflammatory response.

Complement activation results in the production of the anaphylatoxin chemokines C3a and C5a, which attract more neutrophils and macrophages. These in turn are further activated by immune complexes binding to their Fc receptors to secrete proinflammatory chemokines and cytokines, prostaglandins, and proteases. Proteases attack the basement membrane proteins collagen and elastin, as well as cartilage.

Tissue damage is further mediated by oxygen free radicals released by the activated neutrophils. In addition, immune complexes interact with platelets and induce the formation of tiny clots.

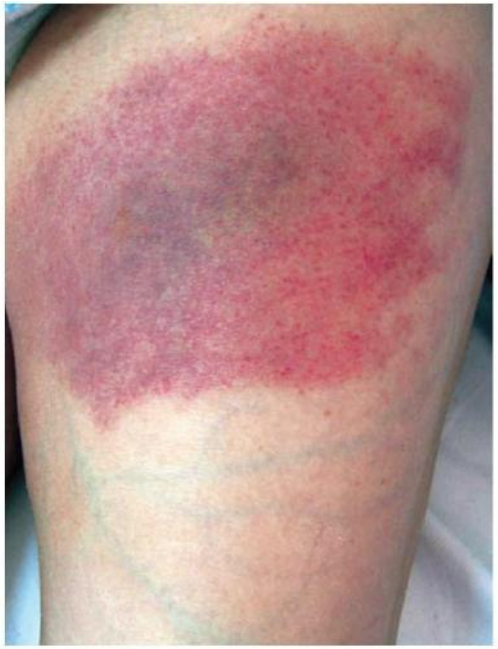
Complex deposition in the tissues can give rise to symptoms such as fever, urticaria (rashes), joint pain, lymph node enlargement, and protein in the urine. The resulting inflammatory lesion is referred to as vasculitis if it occurs in a blood vessel, glomerulonephritis if it occurs in the kidneys, or arthritis if it occurs in the joints.

Formation of circulating immune complexes contributes to the pathogenesis of number of conditions involving type III hypersensitivity reactions

Autoimmune diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Drug reactions
Allergies to penicillin and sulfonamides
Infectious diseases
Poststreptococcal glomerulonephritis
Meningitis
Hepatitis
Mononucleosis
Malaria
Trypanosomiasis

Arthus reactions are localized type III hypersensitivity reactions

One example of a localized type III hypersensitivity reaction has been used extensively as an experimental tool. If an animal or human subject is injected intradermally with an antigen to which large amounts of circulating antibodies exist (or have been recently introduced by intravenous injections), antigen will diffuse into the walls of local blood vessels and large immune complexes will precipitate close to the injection site. This initiates an inflammatory reaction that peaks approximately 4 to 10 hours postinjection and is known as an Arthus reaction. Inflammation at the site of an Arthus reaction is characterized by swelling and localized bleeding, followed by fibrin deposition.

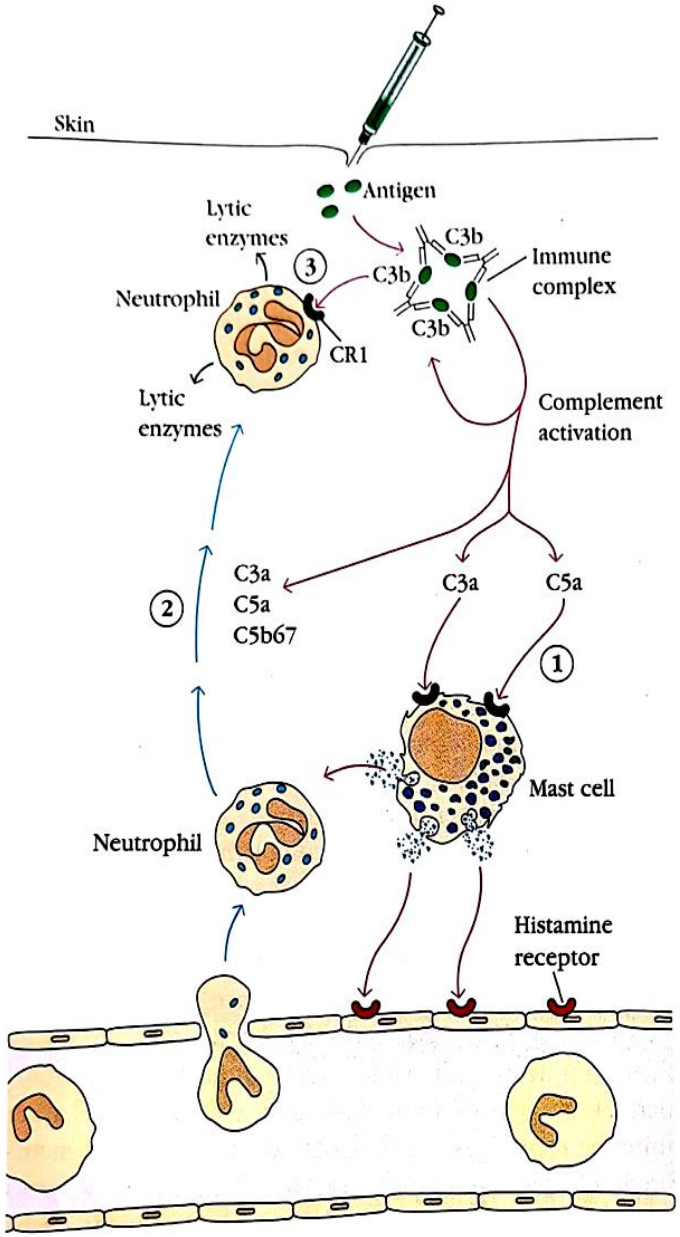


An Arthus reaction. This photograph shows an Arthus reaction on the thigh of a 72-year-old woman.
This occurred at the site of injection of a hemotherapeutic drug, 3 to 4 hours after the patient received a second injection (15 days after the first).
This response was accompanied by fever and significant discomfort.

A sensitive individual may react to an insect bite with a rapid, localized type I allergic reaction, which can be followed, some 4 to 10 hours later, by the development of a typical Arthus reaction, characterized by pronounced erythema and edema.

Intrapulmonary Arthus-type reactions in the lung induced by bacterial spores, fungi, or dried fecal proteins in people with antibodies to these antigens 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 Diseases is caused due to inhalation of thermophilic actinomycetes from moldy hay.
Pigeon fancier's disease results from inhalation of a serum protein in dust derived from dried pigeon feces.



Injection of an antigen intradermally or subcutaneously into an animal that has circulating antibody specific for that antigen leads to formation of localized immune complexes.

Neutrophils adhere to the vascular endothelium and then migrate to the site of immune complex deposition.

As the reaction continues localized damage results in accumulation of fluid (edema) and red blood cells (erythema).

Development of localized Arthus reaction (Type III hypersensitivity reaction.

Complement activation initiated by immune complexes (Classical pathway) produces complement intermediates that

1. Mediate mast cell degranulation
2. Chemotactically attract neutrophils
3. Stimulate release of lytic enzymes from neutrophils trying to phagocytose C3b-coated immune complexes.

Type IV or Delayed-Type Hypersensitivity (DTH)

When some subpopulations of activated T_H cells encounter certain types of antigens, they secrete cytokines that induce a localized imflammatory reaction called **delayed type hypersensitivity (DTH).), It is the** only hypersensitivity category that is purely cell mediated rather than antibody mediated

The hallmarks of a type IV reaction are its initiation by T cells (as distinct from antibodies), the delay required for the reaction to develop (usually 1 to 2 days), and the recruitment of macrophages (as opposed to neutrophils or eosinophils) as the primary cellular component of the infiltrate that surrounds the site of inflammation.

In1890, Robert Koch observed that individuals infected with Mycobacterium tuberculosis developed a localized inflammatory response when injected intradermally (i.e., via the skin) with a filtrate derived from a mycobacterial culture. He therefore named this localized skin reaction **a tuberculin reaction**. Later, as it became apparent that a variety of other antigens could induce this cellular Response **, its name was changed to delayed-type, or type IV, hypersensitivity.**

Intracellular pathogens and contact antigens that induce delayed-type (type IV) hypersensitivity

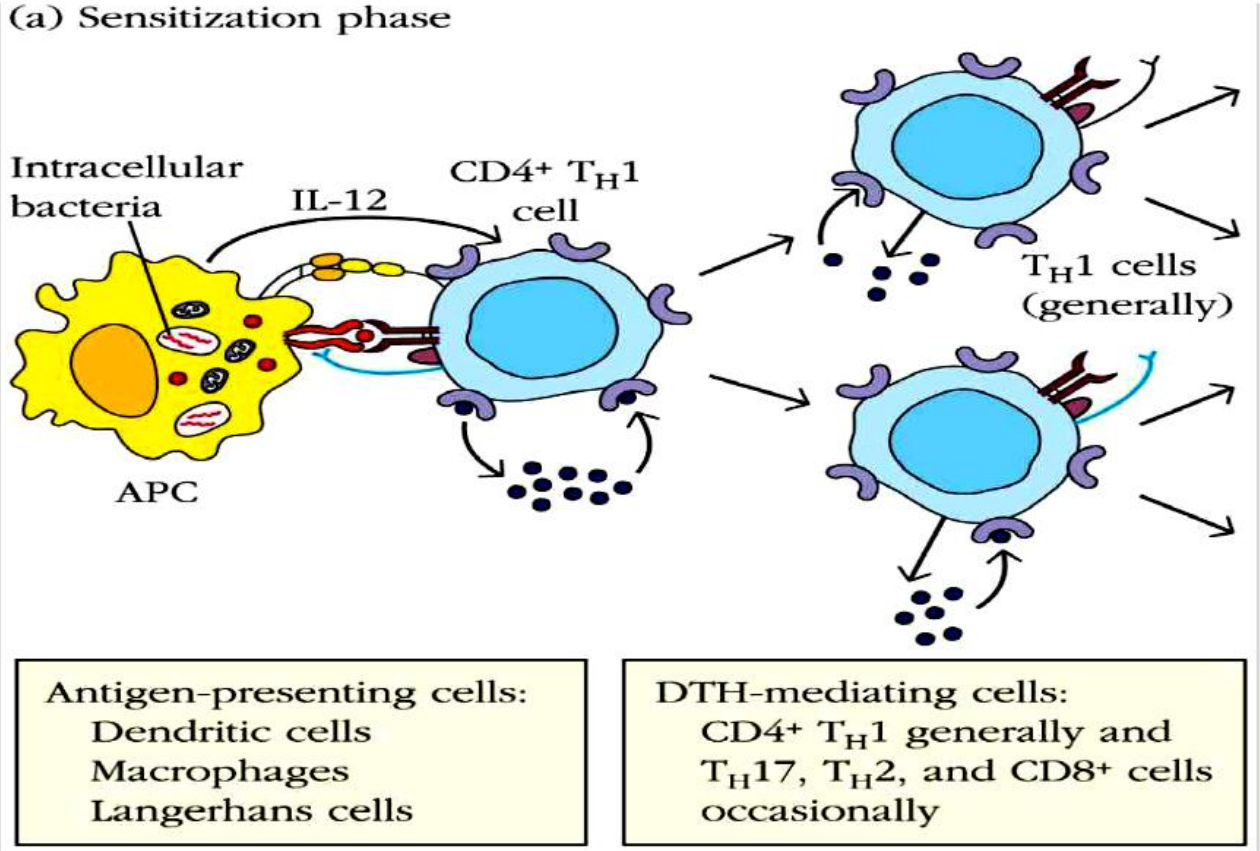
Intracellular bacteria
- *Mycobacterium tuberculosis*
- *Mycobacterium leprae*
- *Listeria monocytogenes*
- *Brucella abortus*

Intracellular fungi
- *Pneumocystis carinii*
- *Candida albicans*
- *Histoplasma capsulatum*
- *Cryptococcus neoformans*

Intracellular parasites
- *Leishmania* sp.

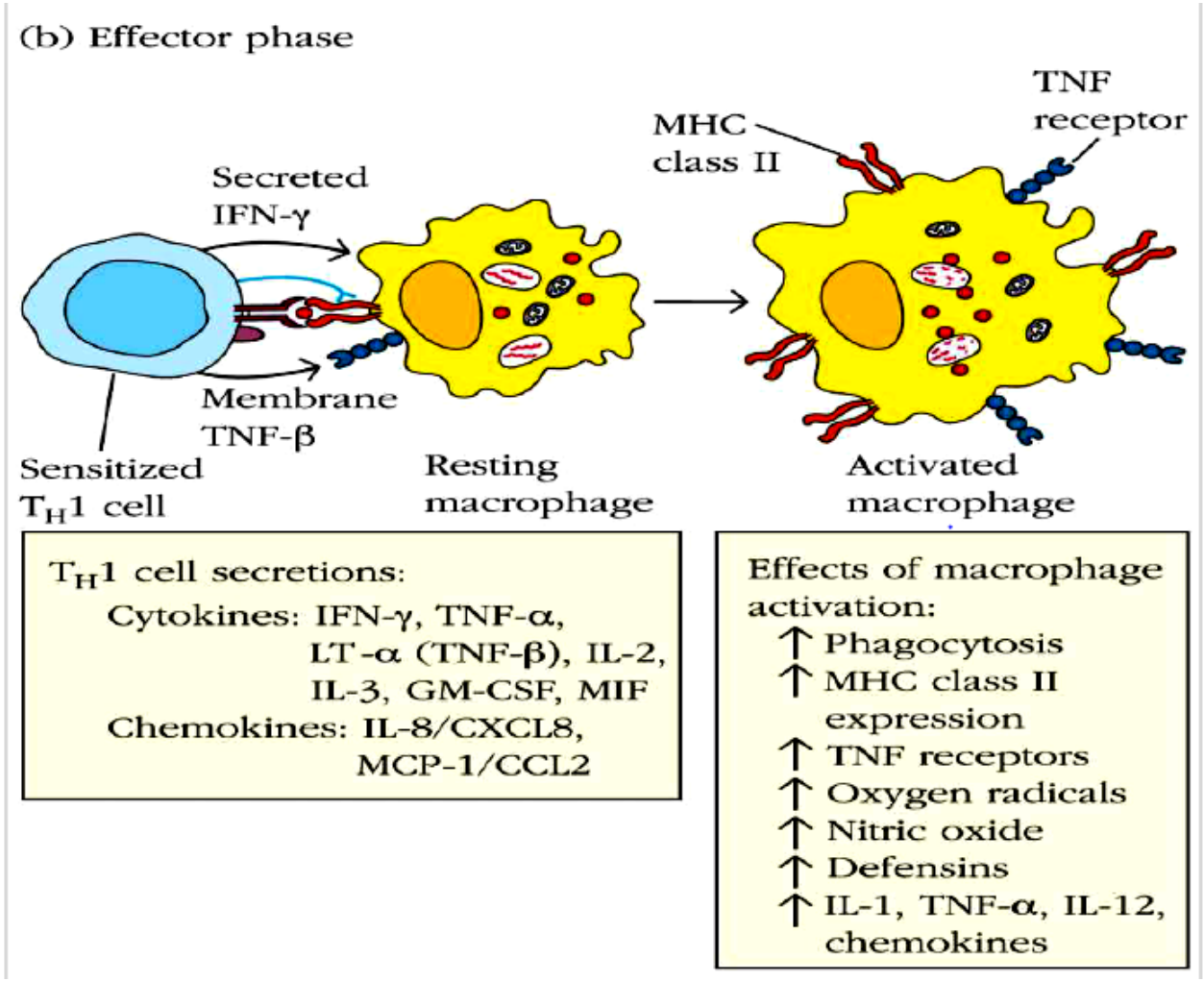
Intracellular viruses
- Herpes simplex virus
- Variola (smallpox)
- Measles virus

Contact antigens
- Picrylchloride
- Hair dyes
- Nickel salts
- Poison ivy
- Poison oak



The DTH response.

(a) In the sensitization phase after initial contact with antigen (e.g., peptides derived from intracellular bacteria), naïve CD4 cells proliferate and differentiate into T_H1 cells. Cytokines secreted by these T cells are indicated by the black dots.



b) In the effector phase after subsequent exposure of sensitized effector T cells to antigen, T_H 1 cells secrete a variety of cytokines and chemokines, including IFN-γ. These factors attract and activate macrophages and other nonspecific inflammatory cells. Activated macrophages are more effective in presenting antigen, thus perpetuating the DTH response, and function as the primary effector cells in this reaction. The T_H 17 helper T-cell subset and CD8 T cells also contribute to DTH responses.

The heightened phagocytic activity and the buildup of lytic enzymes from macrophages in the area of infection lead to nonspecific destruction of cells and thus of any intracellular pathogens.
in some cases, and especially if the antigen is not easily cleared, a prolonged DTH response can develop that becomes destructive to the host, causing a visible granulomatous reaction.

Granulomas develop when continuous activation of macrophages induces them to adhere closely to one another. Under these conditions, macrophages assume an epithelioid shape and sometimes fuse to form multinucleated giant cells.

These giant cells displace the normal tissue cells, forming palpable nodules, and releasing high concentrations of lytic enzymes, which destroy surrounding tissue. The granulomatous response can damage blood vessels and lead to extensive tissue necrosis.

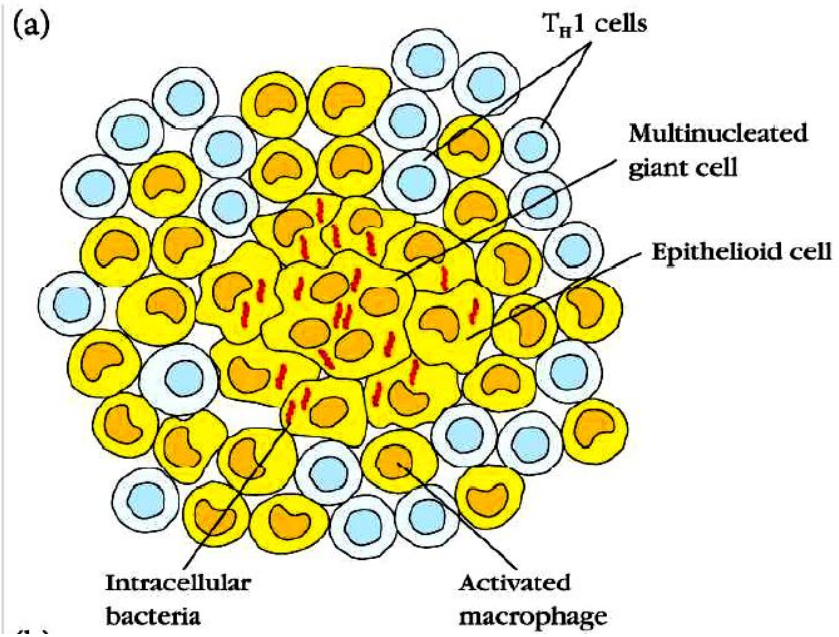
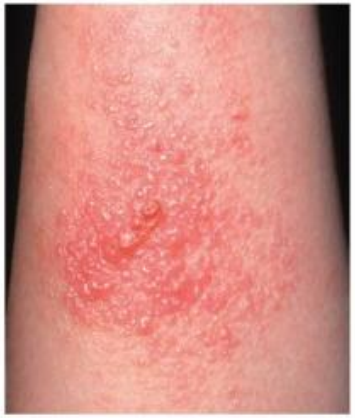


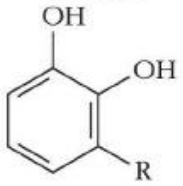
Fig. A prolonged DTH response can lead to formation of a granuloma, a nodule-like mass. (a) Lytic enzymes released from activated macrophages in a granuloma can cause extensive tissue damage.

(a)



(b)

Urushiol



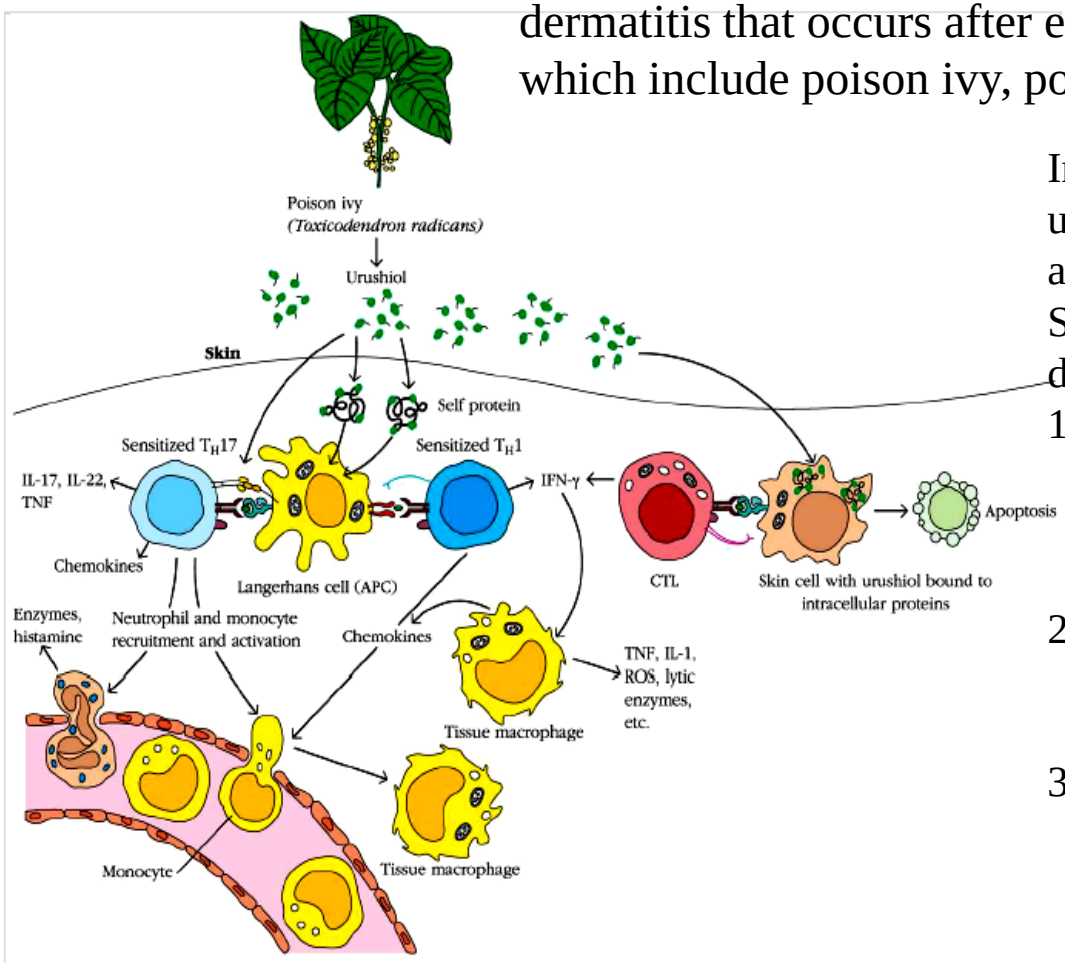
R = $(CH_2)_{14}CH_3$ or
R = $(CH_2)_7CH{=}CH(CH_2)_5CH_3$ or
R = $(CH_2)_7CH{=}CHCH_2CH{=}CH(CH_2)_2CH_3$ or
R = $(CH_2)_7CH{=}CHCH_2CH{=}CHCH{=}CHCH_3$ or
R = $(CH_2)_7CH{=}CHCH_2CH{=}CHCH_2CH{=}CH_2$

Poison ivy causes contact dermatitis due to its toxin, urushiol.

(a) Poison ivy and the contact dermatitis form of DTH that it causes in many people.

(b) The structures of the alkylcatechols with varying R-groups, alkyl chains of 15–17 carbon atoms, that comprise the urushiol toxin family.

The most common type IV hypersensitivity is the contact dermatitis that occurs after exposure to Toxicodendron species, which include poison ivy, poison oak, and poison sumac.



Induction of contact dermatitis by urushiol can be mediated by T_H 1, T_H17, and CTL effector T cells.

Skin DTH reactions are caused by three different effector T cells:

1. effector T_H1 cells that recognize urushiol-modified peptides bound to MHC class II proteins on Langerhans cells;
2. effector T_H 17 cells that recognize urushiol bound to CD1a on Langerhans cells; and
3. CD8 CTL effector cells that recognize urushiol-modified peptides presented by MHC class I proteins on skin cells.

After activation, the T cells produce chemokines and cytokines that recruit and activate macrophages and neutrophils to release inflammatory cytokines, enzymes, and ROS that cause local tissue damage. CTLs may also kill skin cells expressing urushiol-modified peptides bound to MHC class I proteins.