UNIVERSITATEA DE STAT DE MEDICINĂ
ȘI FARMACIE „NICOLAE TESTEMIȚANU”
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Pathologic immune reactions: Hypersensitivity reactions Autoimmunity and autoimmune diseases

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Hypersensitivity (Hypersensibility) = Immune Response which cause tissue lessions

- Disorders caused by immune responses are called **hypersensitivity diseases**.
- This term arose from the clinical definition of immunity as sensitivity, which is based on the observation that an individual who has been exposed to an antigen exhibits a detectable reaction, or is sensitive, to subsequent encounters with that antigen

According to classification criteria:

- Onset
- Molecules or Cells involved

Immediate hypersensitivity (minutes ---------2 hours) – umoral (IgE, IgG/M)

Delayed hypersensitivity (days) –cellular type (Th1 response)

Immune responses that are the cause of hypersensitivity diseases may be specific for antigens from different sources:

- ***Autoimmunity: reactions against self antigens*.** Failure of the normal mechanisms of self-tolerance results in T cell and B cell reactions against one's own cells and tissues that are called **autoimmunity**

- ***Reactions against microbes.*** Immune responses against microbial antigens may cause disease if the reactions are excessive or the microbes are unusually persistent

- ***Reactions against nonmicrobial environmental antigens*** (pollen, HDM, fungal allergens, animal Ag etc)- allergic diseases

Types of immune responses (Hypersensitivity Diseases) (Gell-Coombs classification)

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

TABLE 19-1 Classification of Hypersensitivity Diseases

Type of Hypersensitivity	Pathologic Immune Mechanisms	Mechanisms of Tissue Injury and Disease
Immediate: type I	IgE antibody, T_H2 cells	Mast cells, eosinophils, and their mediators (vasoactive amines, lipid mediators, cytokines)
Antibody–mediated: type II	IgM, IgG antibodies against cell surface or extracellular matrix antigens	Opsonization and phagocytosis of cells Complement- and Fc receptor–mediated recruitment and activation of leukocytes (neutrophils, macrophages) Abnormalities in cellular functions, e.g., hormone receptor signaling, neurotransmitter receptor blockade
Immune complex– mediated: type III	Immune complexes of circulating antigens and IgM or IgG antibodies	Complement- and Fc receptor–mediated recruitment and activation of leukocytes
T cell–mediated: type IV	1. $CD4^+$ T cells (T_H1 and T_H17 cells) 2. $CD8^+$ CTLs	1. Cytokine-mediated inflammation 2. Direct target cell killing, cytokine-mediated inflammation

Type 1 hypersensitivity reaction

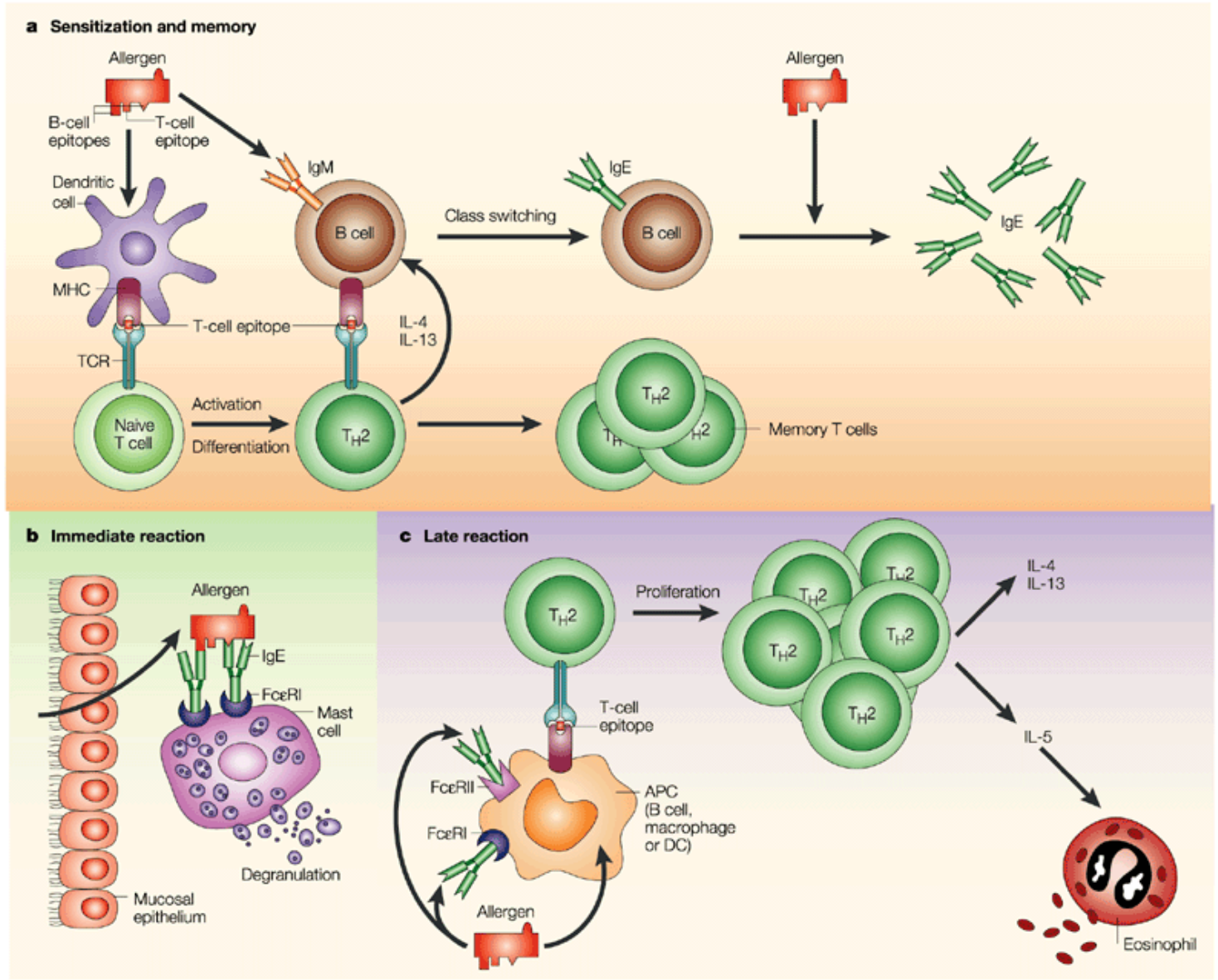
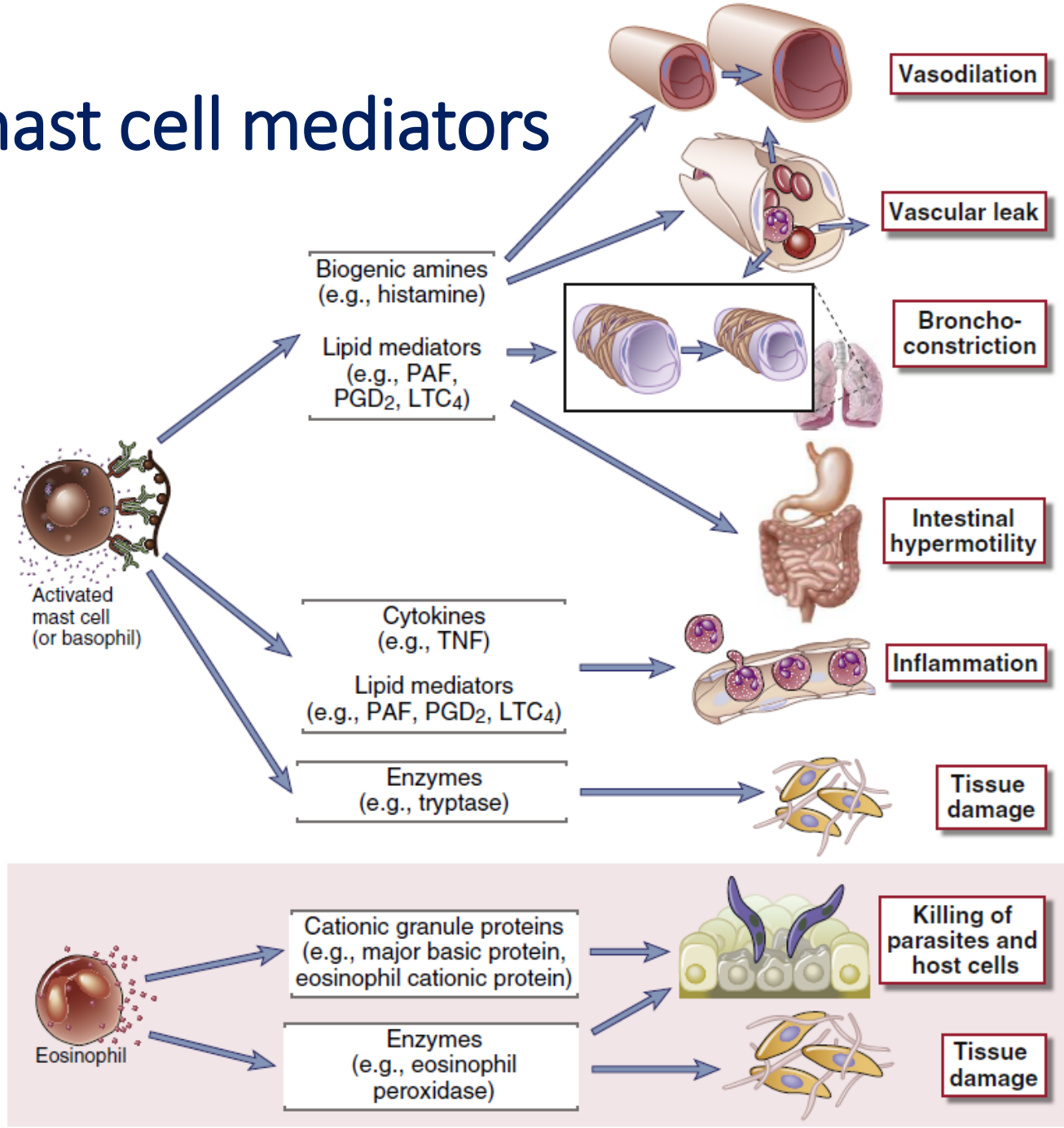


TABLE 15-3 Principal mediators involved in type I hypersensitivity

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 CAMs on venular endothelial cells
IL-4 and IL-13	Increased IgE production
IL-3, IL-5, IL-6, IL-10, TGF-β, and GM-CSF	Various effects (see Table 12-1)

Biological effects of mast cell mediators

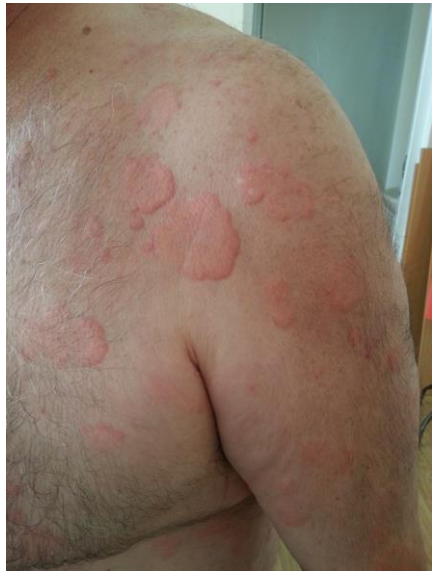


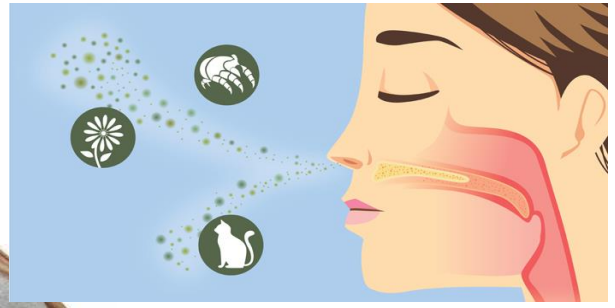
Clinical manifestation of HSR type I

Allergen: inhaled, ingested, parenteral

Local - mast cells accumulate in the airways, intestinal walls, tegument → RHS type I occur at these levels (asthma, urticaria, AE, allergic rhinitis)

Systemic - anaphylaxis, vasodilation and fluid loss → shock

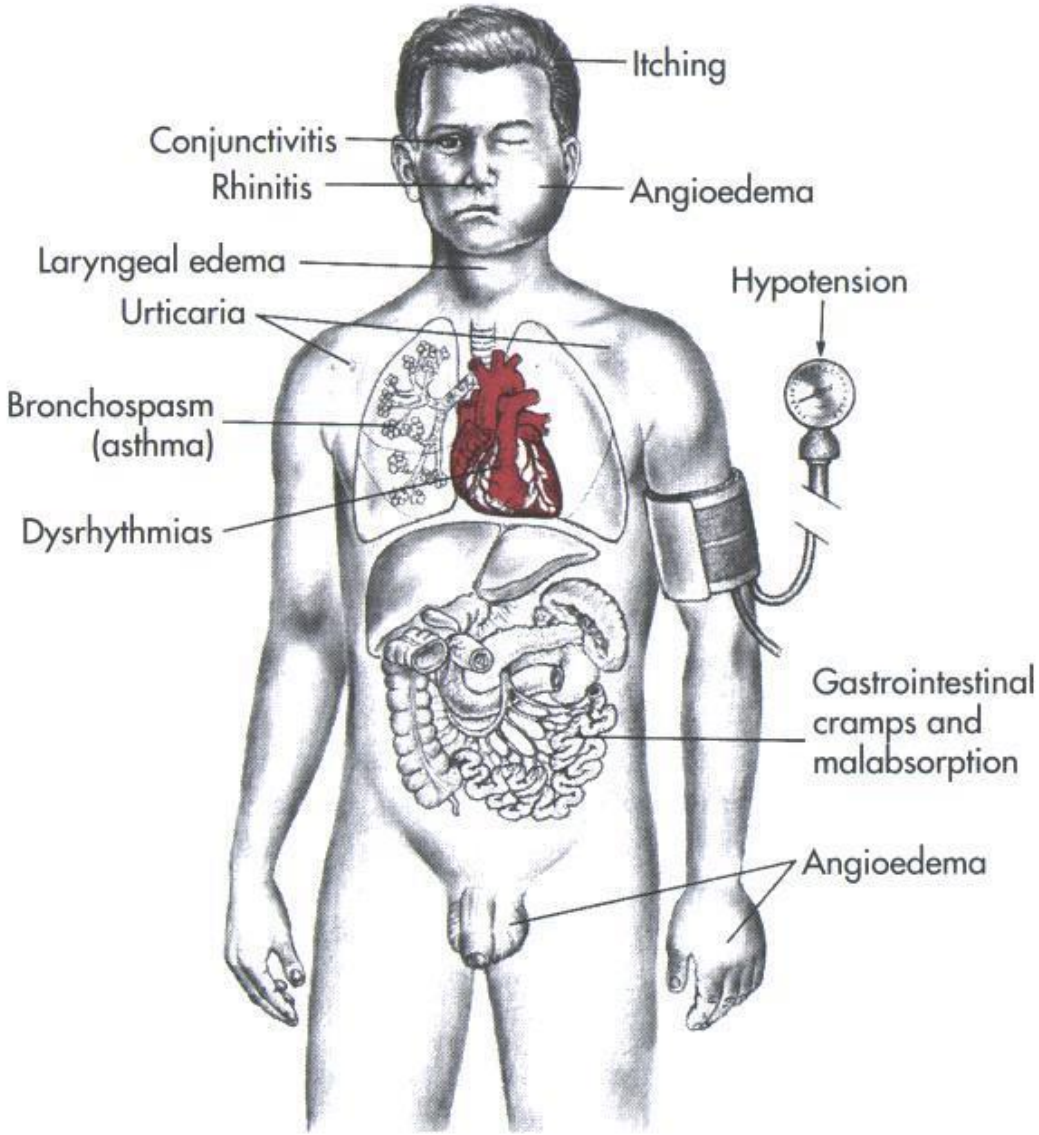


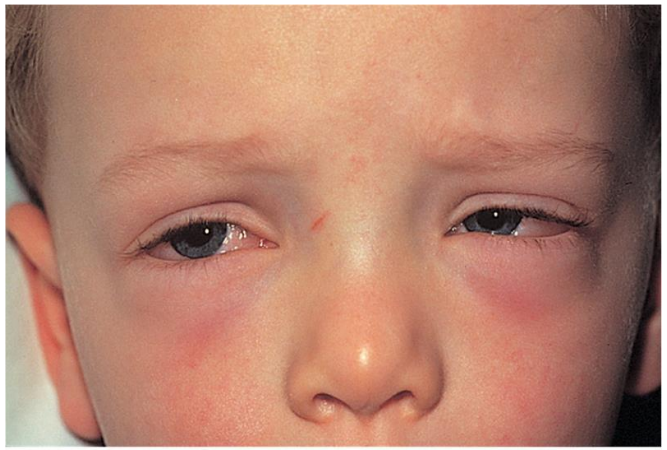


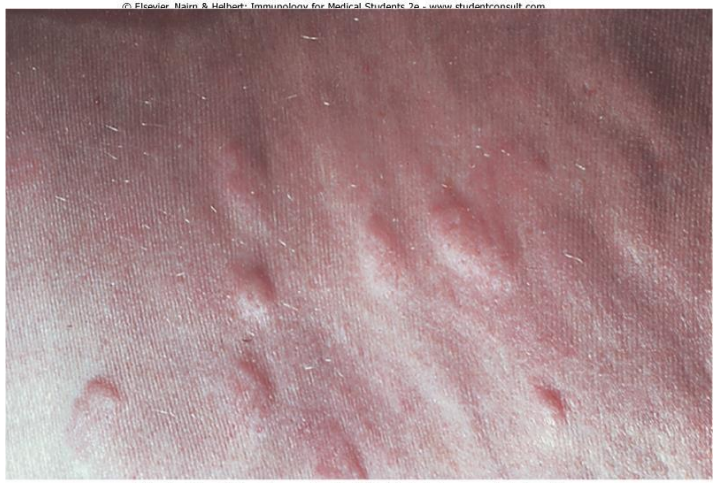
Local and systemic IgE-mediated allergic manifestation

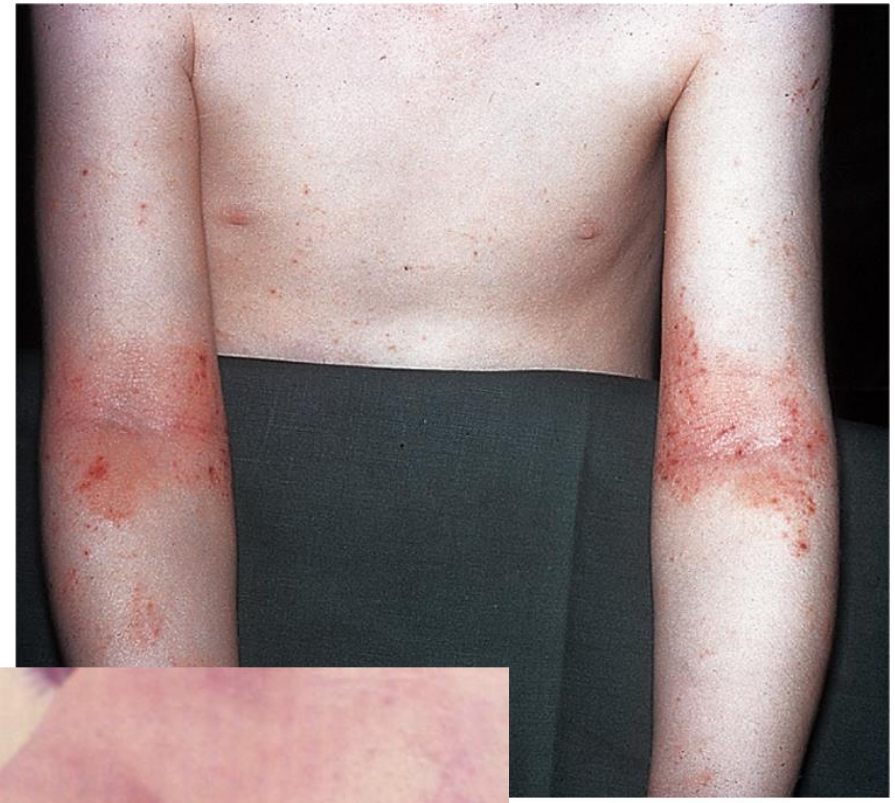
IgE-mediated allergic reactions			
Syndrome	**Common allergens**	**Route of entry**	**Response**
Systemic anaphylaxis	Drugs Serum Venoms Peanuts	Intravenous (either directly or following oral absorption into the blood)	Edema Increased vascular permeability Tracheal occlusion Circulatory collapse Death
Acute urticaria (wheal-and-flare)	Animal hair Insect bites Allergy testing	Through skin	Local increase in blood flow and vascular permeability
Allergic rhinitis (hay fever)	Pollens (ragweed, timothy, birch) Dust-mite feces	Inhalation	Edema of nasal mucosa Irritation of nasal mucosa
Asthma	Danders (cat) Pollens Dust-mite feces	Inhalation	Bronchial constriction Increased mucus production Airway inflammation
Food allergy	Tree nuts Peanuts Shellfish Milk Eggs Fish	Oral	Vomiting Diarrhea Pruritis (itching) Urticaria (hives) Anaphylaxis (rarely)

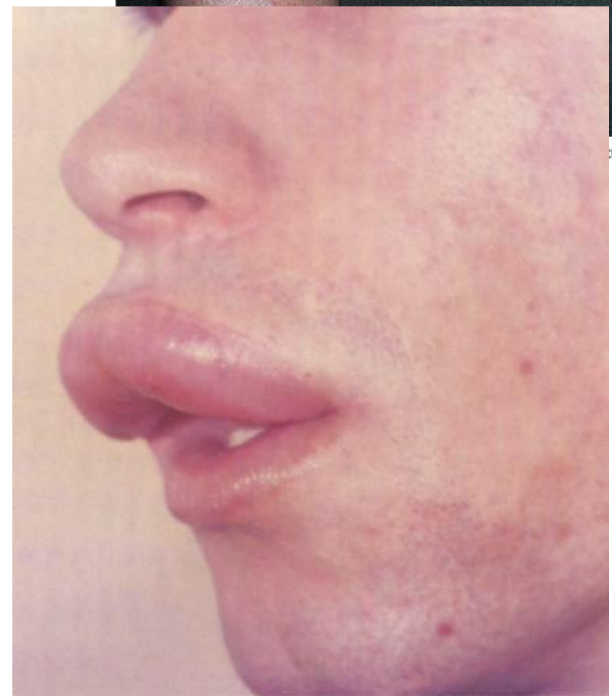
Figure 12-1 Immunobiology, 6/e. (© Garland Science 2005)











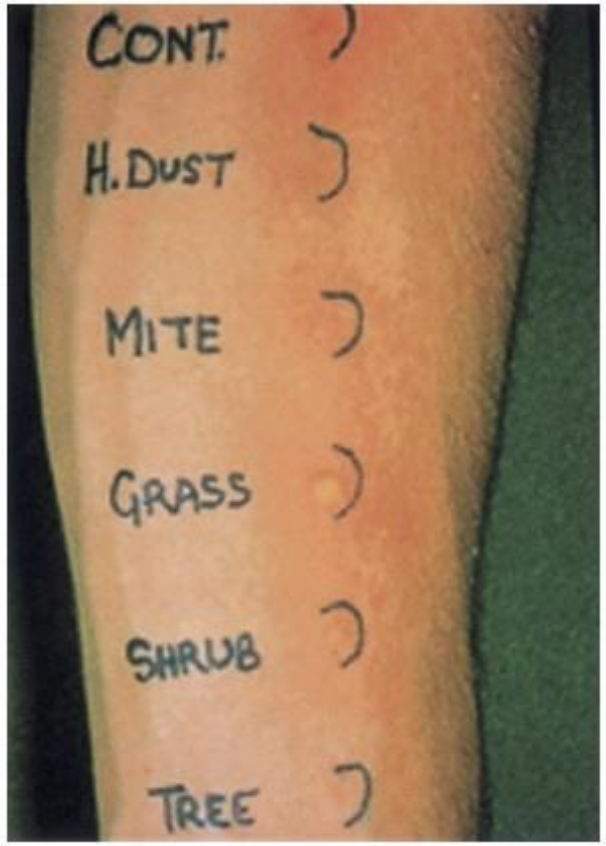
Diagnostic of HSR type I

Polen de ierburi

Știr		Ama r		≤ 0,10
Ambrozie		Amb a		7,93
		Amb a 1	Pectat-liază	30,72
		Amb a 4	Defensina din plante	≤ 0,10
Pelin negru		Art v		≤ 0,10
		Art v 1	Defensina din plante	≤ 0,10
		Art v 3	nsLTP	≤ 0,10

Acarieni

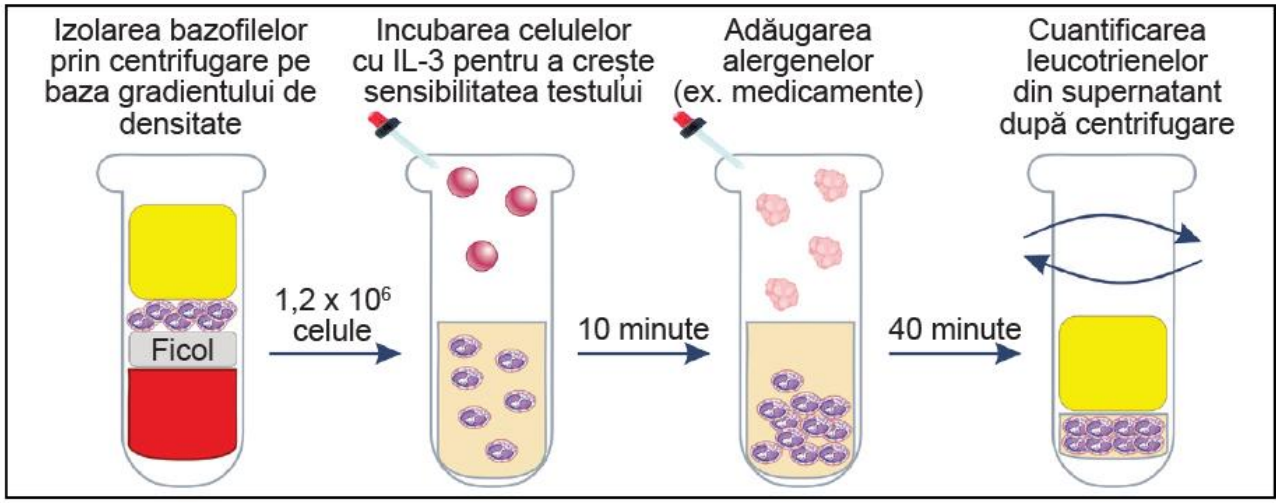
Dermatophagoides farinae		Der f 1	Cistein-protează	≤ 0.10
		Der f 2	Familia NPC 2	12.69
Dermatophagoides pteronyssinus		Der p 1	Cistein-protează	≤ 0.10
		Der p 2	Familia NPC 2	12.98
		Der p 5	Necunoscut	≤ 0.10

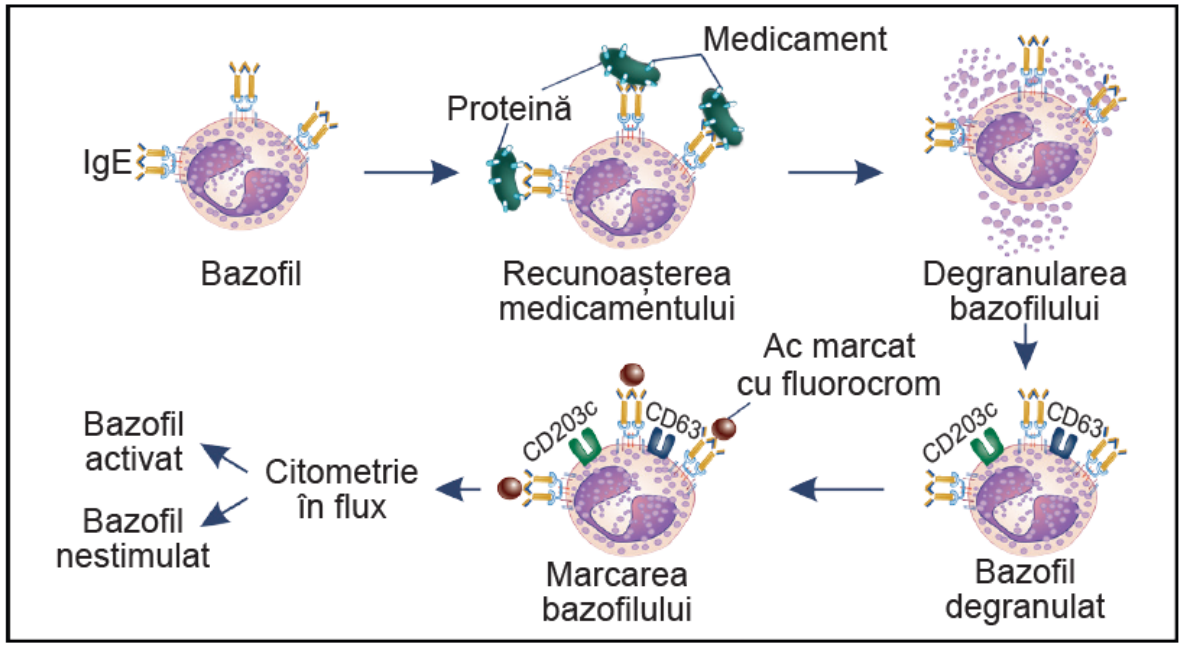


Basophil degranulation /activation test (BAT)

The basophil activation test (BAT) is an *in vitro* functional assay that measures by flow cytometry the degree of basophil degranulation after stimulation with an allergen

Basophil degranulation test





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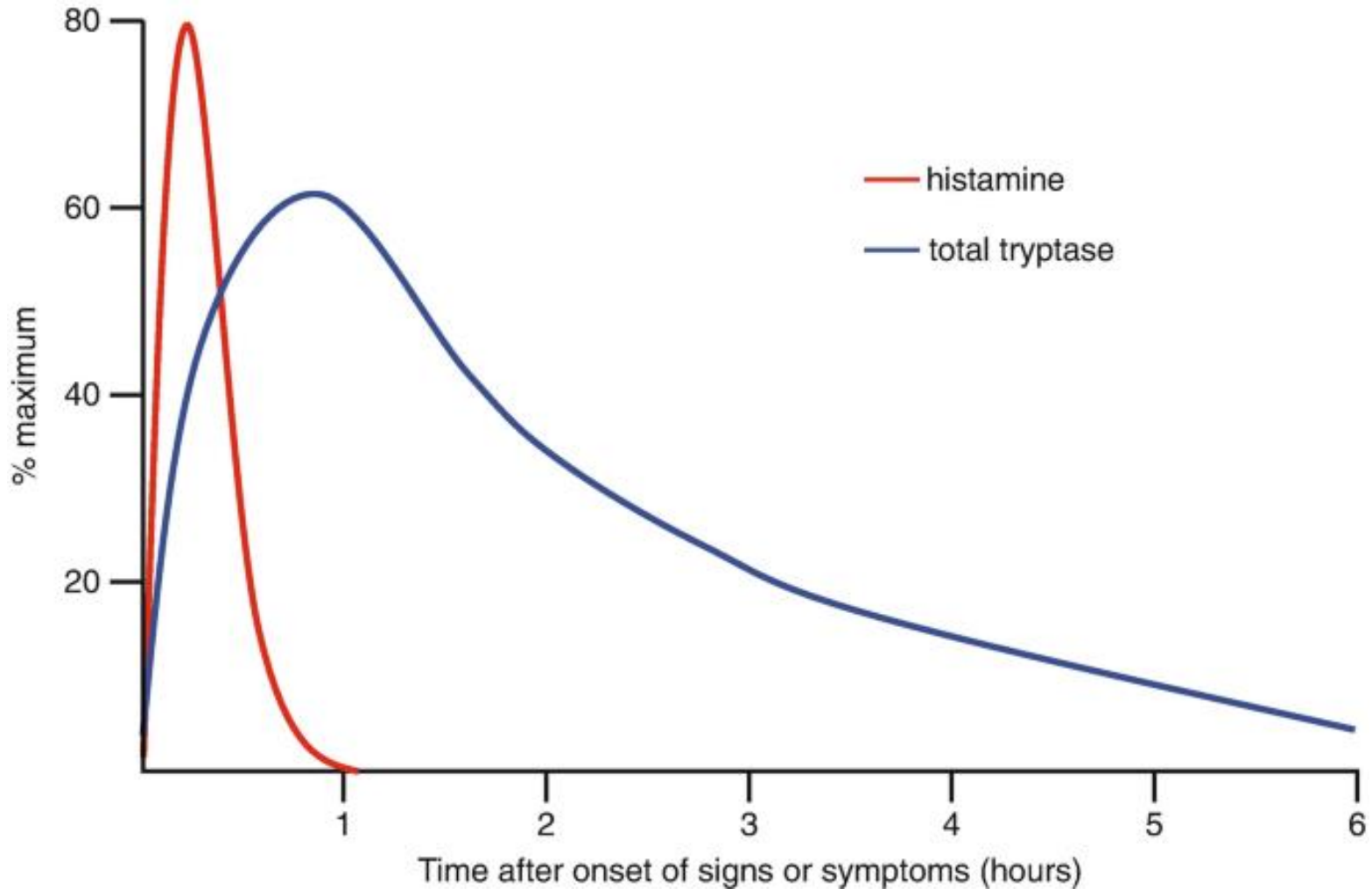
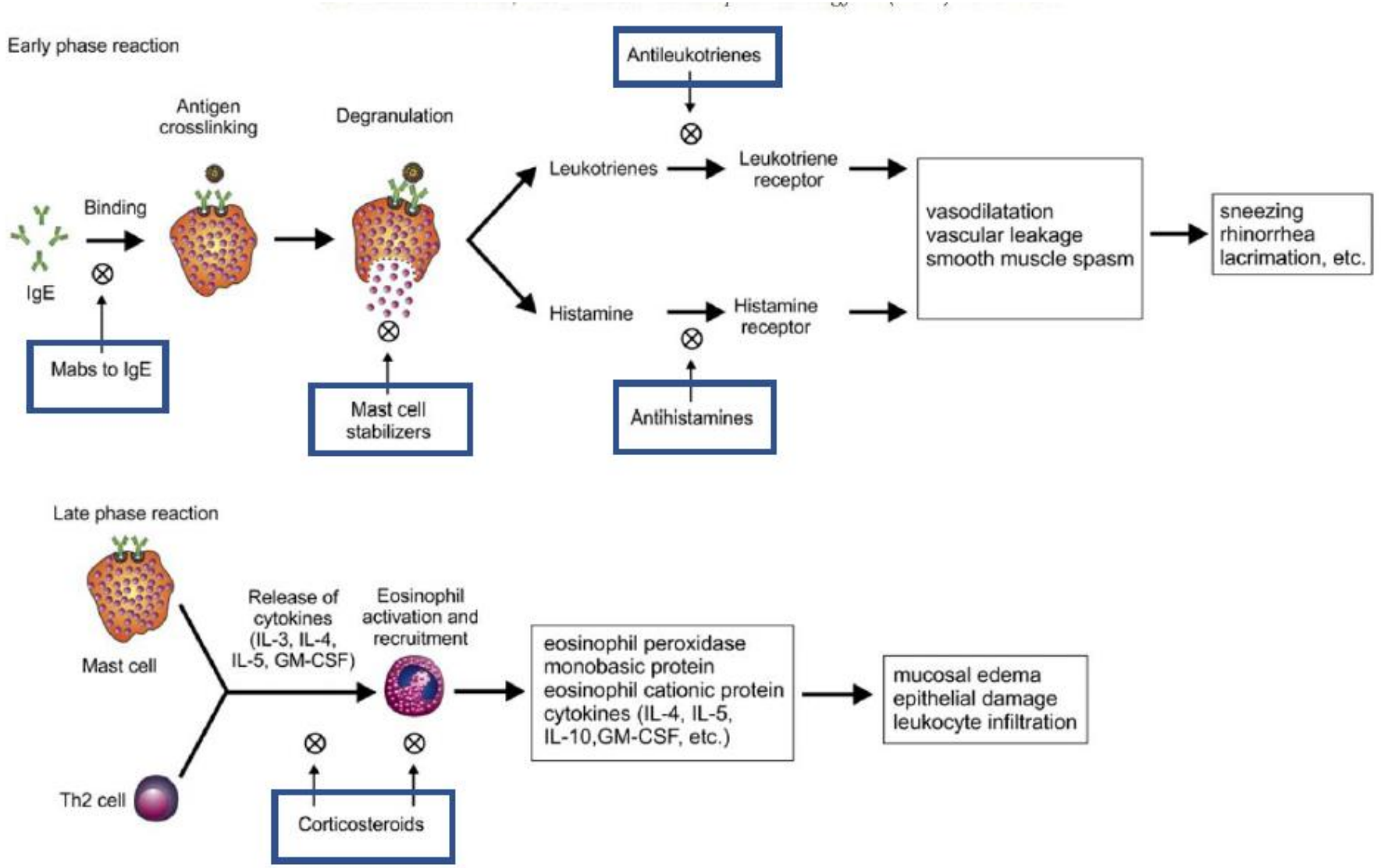
Histamine and serum triptase



Treatment HSR I. Drug treatment of allergy



Type 2 hypersensitivity reaction (cytotoxic)

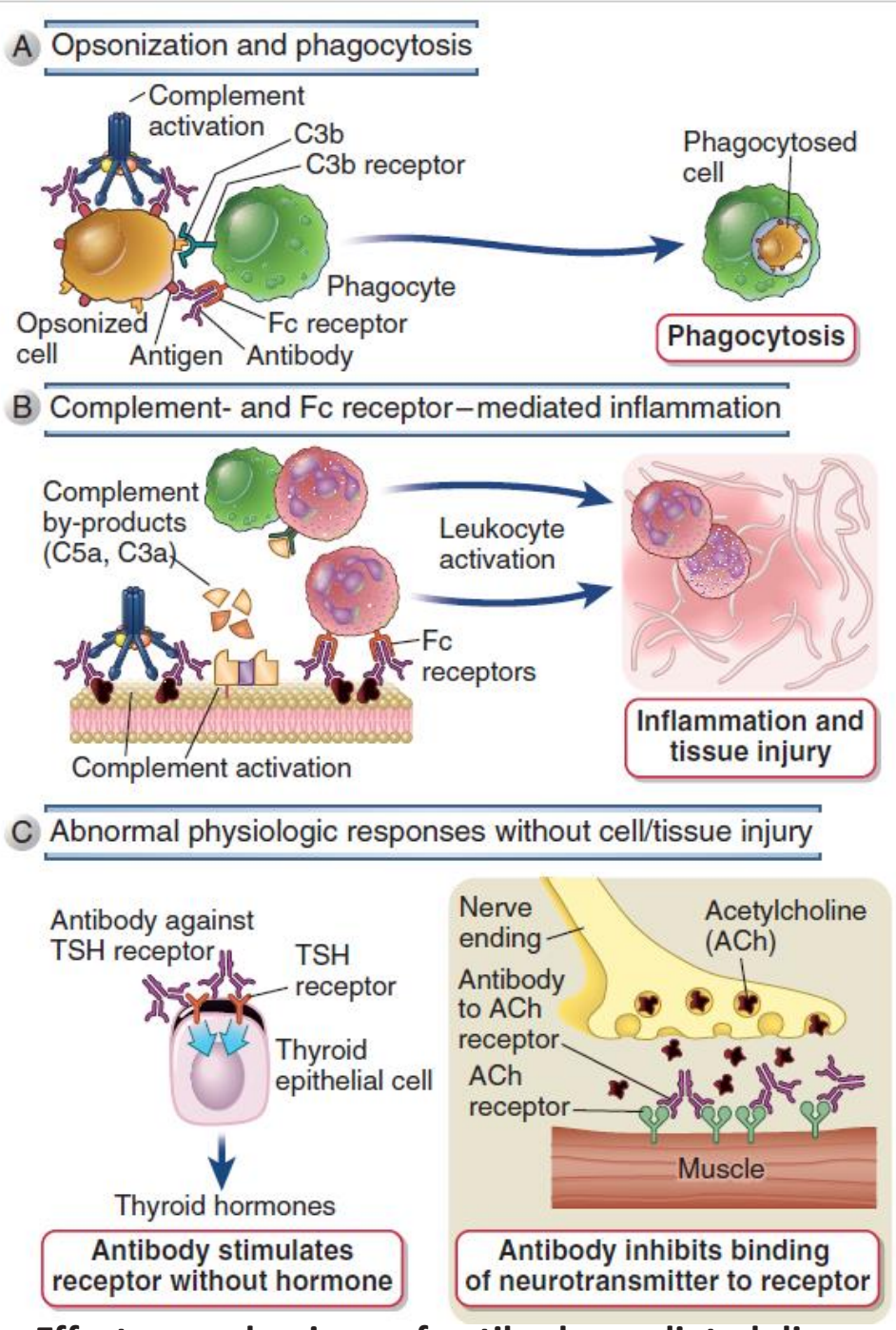
Type II hypersensitivity reaction refers to an antibody-mediated immune reaction in which antibodies (IgG or IgM) are directed against cellular or extracellular matrix antigens, resulting in cellular destruction, functional loss, or tissues damage.

Type 2 hypersensitivity reaction (cytotoxic)

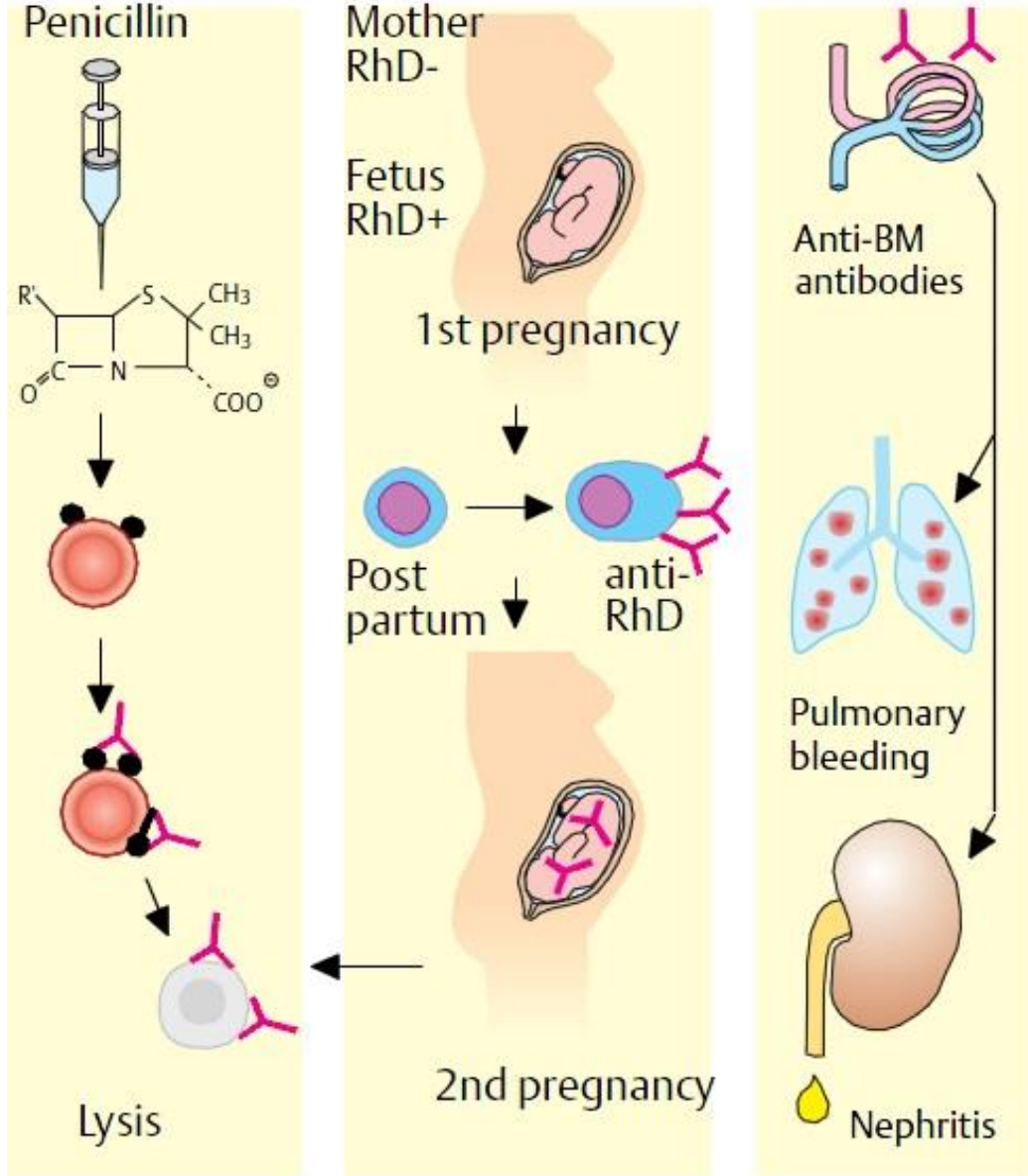
Ab =IgM and IgG

- Onset (1–3 hours) after Ag exposure
- Time (10–15 hours)

- Ag on cell surface
- IC formation by adding Ab →ADCC, Complement activation →cell lysis



Effector mechanisms of antibody-mediated disease



Type II: Cytotoxic antibody reactions

Forme clinice ale RHS de tip II

Sinteza anticorpilor citotoxici poate avea diferite mecanisme:

- **aloimunizare**, prin declanșarea unui RIU are loc formarea Ac anti celule sau țesuturi străine (non-*self*), de exemplu, post-transplant sau conflictul Rh materno-fetal;

- **autoimunizare**, formarea Ac față de celulele *self*, prin mecanisme de dereglare a toleranței față de *self*. Exemple fiind unele boli autoimune: LES, anemii autoimune, tiroidita Hashimoto, purpura trombocitopenică autoimună idiopatică.

- după administrarea unor **medicamente cu rol de haptenă**, care se vor atașa de suprafața celulelor umane, rezultând distrugerea lor (trombocitopeniile postmedicamentoase).

TABLE 19.2 Examples of Diseases Caused by Cell- or Tissue-Specific Antibodies

Disease	Target Antigen	Mechanisms of Disease	Clinicopathologic Manifestations
Autoimmune hemolytic anemia	Erythrocyte membrane proteins	Opsonization and phagocytosis of erythrocytes, complement-mediated lysis	Hemolysis, anemia
Autoimmune thrombocytopenic purpura	Platelet membrane proteins (gpIIb-IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (desmoglein)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin blisters (bullae)
Vasculitis caused by ANCA	Neutrophil granule proteins, presumably released from activated neutrophils	Neutrophil degranulation and inflammation	Vasculitis
Goodpasture syndrome	Noncollagenous NC1 protein of basement membrane in glomeruli and lung	Complement- and Fc receptor–mediated inflammation	Nephritis, lung hemorrhage
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding, down modulates receptors	Muscle weakness, paralysis
Graves' disease (hyperthyroidism)	TSH receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor; decreased absorption of vitamin B_{12}	Abnormal erythropoiesis, anemia, neurologic symptoms

ANCA, Anti-neutrophil cytoplasmic antibodies; *TSH,* thyroid-stimulating hormone.

Principii de diagnostic și tratament

Principiile de diagnostic includ documentarea Ac serici sau a Ag de pe celulele țintă.

- Testul Coombs pentru documentarea Ac anti-eritrocite;
- Imunofluorescența pune în evidență Ag tisulare sau Ag fixate cu Ac specifici;
- Dozarea complementului, scăderea valorilor căruia denotă consumul în reacțiile de liză celulară (ex. scăderea C3 în LES).

Principiile de tratament:

- imunosupresoare
- plasmafereză (îndepărtarea Ac citotoxici circulanți)

Type III hypersensitivity reaction

Pathological immune response by circulant immune complexes(type III): Antigens are spread in blood or tissues (often autoAg)

It is due to:

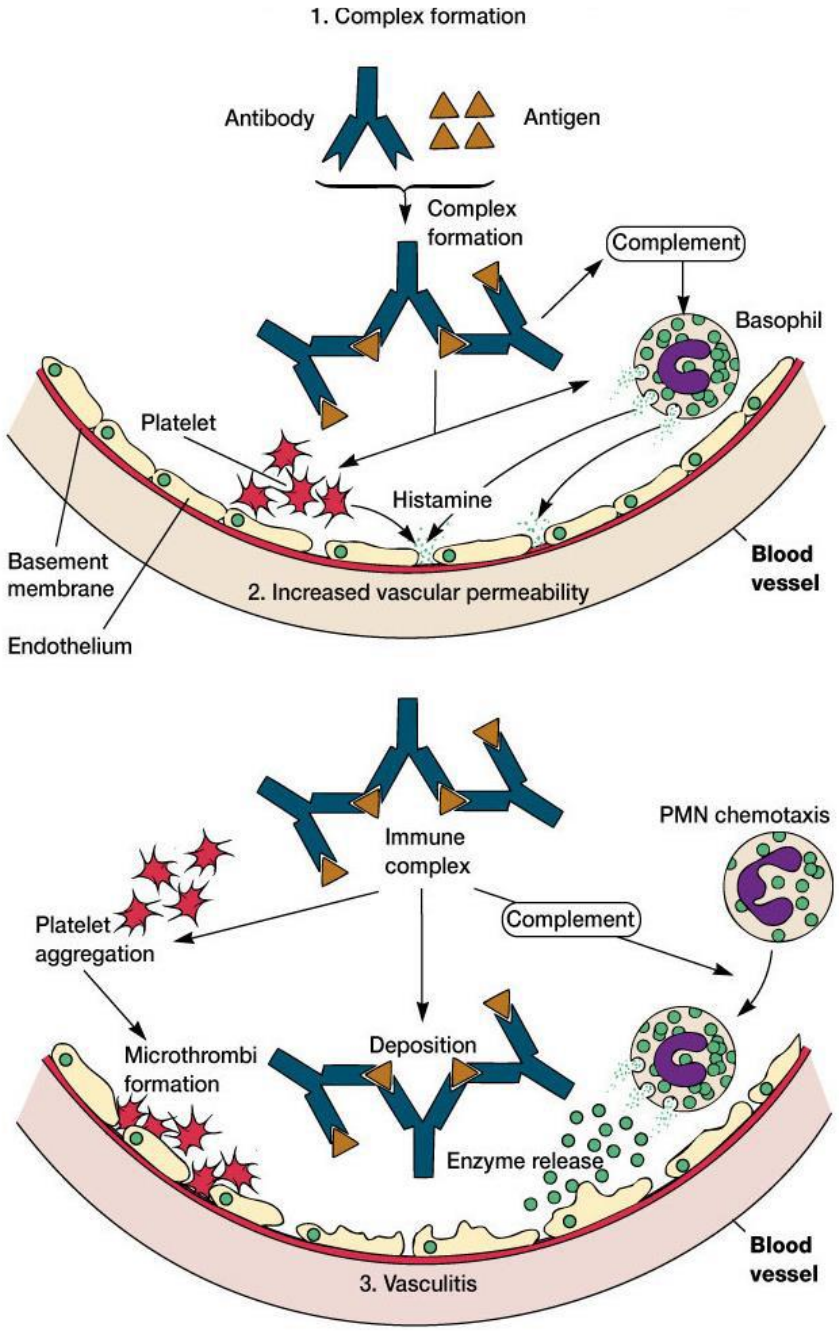
1. Persistent infection / repeated administration of Ag (local or general)
2. Continuous/inefficient synthesis of Abs IgM/IgG determin CIC:

In a balanced concentration of the components, are readily treated by MQ

Small/ soluble complexes (Ag>>>Ac) are difficult purified -> intense inflammation, vascular damage, renal, skin "innocent bystander" (by activation of complement and Leuproteases)

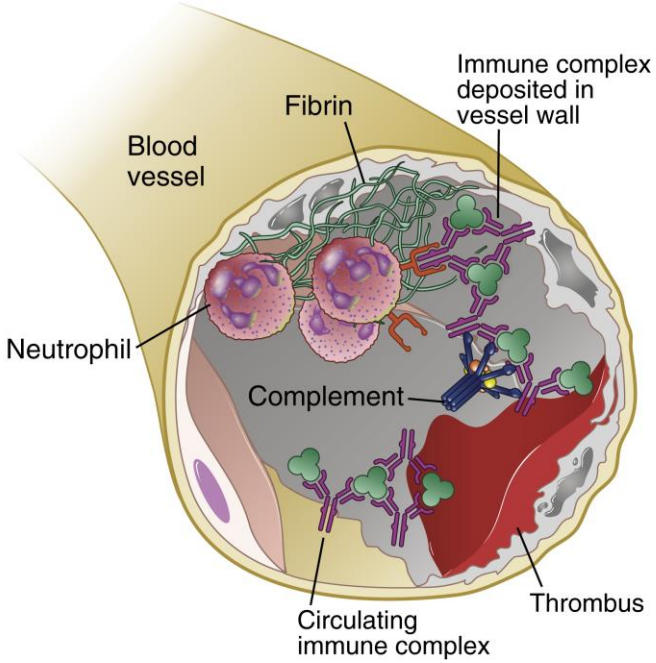
Local inflammatory reaction (Arthus phenomenon) or general (serum sickness)

Characteristic for generalized autoimmune diseases (Lupus, DM, RPA)



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.
- Circulating immune complexes deposit in vessel walls and induce inflammation (vasculitis) and thrombosis.



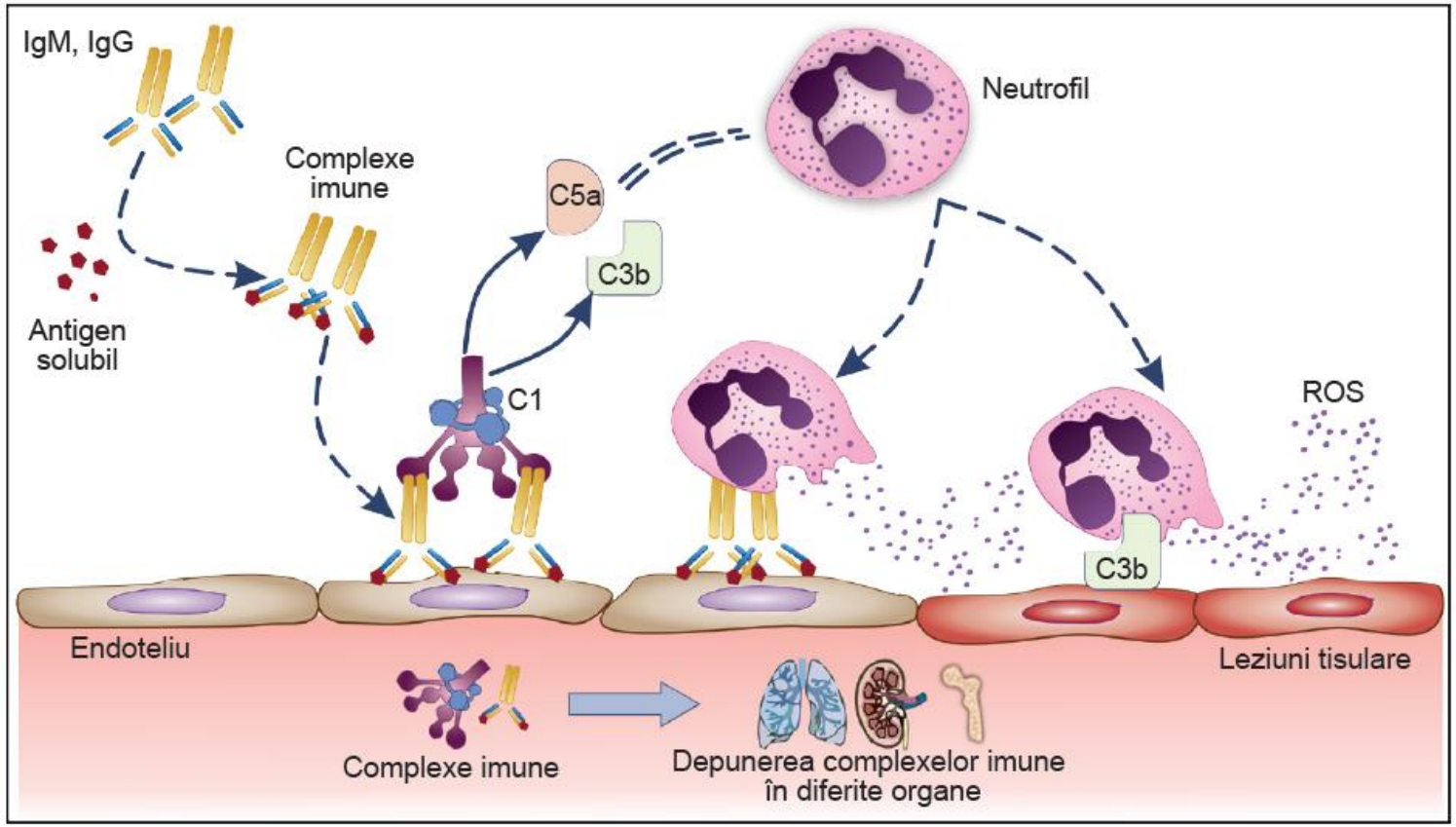
Immune complex–mediated injury

Type 3 hypersensitivity reaction
immune complex formation

Excess immune complexes (circulating or in tissues) → abnormal secondary UIR

Antigens can be:

- microbiene (streptococi, stafilococi, virusurile hepatice, EBV, paraziți)
- autoantigene (auto-Ac în bolile autoimune)
- Ag de mediu (spori de mucegai, veninuri, pulberi, **proteine animale)**



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Forme clinice ale hipersensibilității de tip III

- Complexele circulante antigen-anticorp pot duce la inflamație la locul unde acestea se localizează
- Depinde de dimensiunile CIC, de natura Ag și țesuturile în care se vor depune.

- Depunerile CIC la diferite niveluri:
    - în piele - LES sau reacţia Arthus;
    - rinichi - nefrită lupică;
    - plămâni - ABPA sau pneumonită de hipersensibilitate;
    - vase sanguine - poliarterită;
    - articulaţii - artrită reumatoidă.

- Ag de tip proteine *self* vor declanșa boli autoimune (LES, artrită reumatoidă);
- Medicamentele - reacții de HS la medicamente;
- Proteinele virale, bacteriene sau parazitare - glomerulonefrită post-streptococică, meningită, hepatită, mononucleoză infecţioasă, endocardită bacteriană subacută.

Principii de diagnostic și tratament

Principiile de diagnostic se bazează pe documentarea CIC

- Utilă este și dozarea complementului (o scădere denotă consumul în cadrul unei RHS)
- Dozarea Ig serice (creșterea valorilor IgM și/sau IgG denotă infecții probabile)
- Autoanticorpii

Principiile de tratament:

- medicația imunosupresoare (corticosteroizi și citostatice)
- epurarea CIC prin plasmaferează

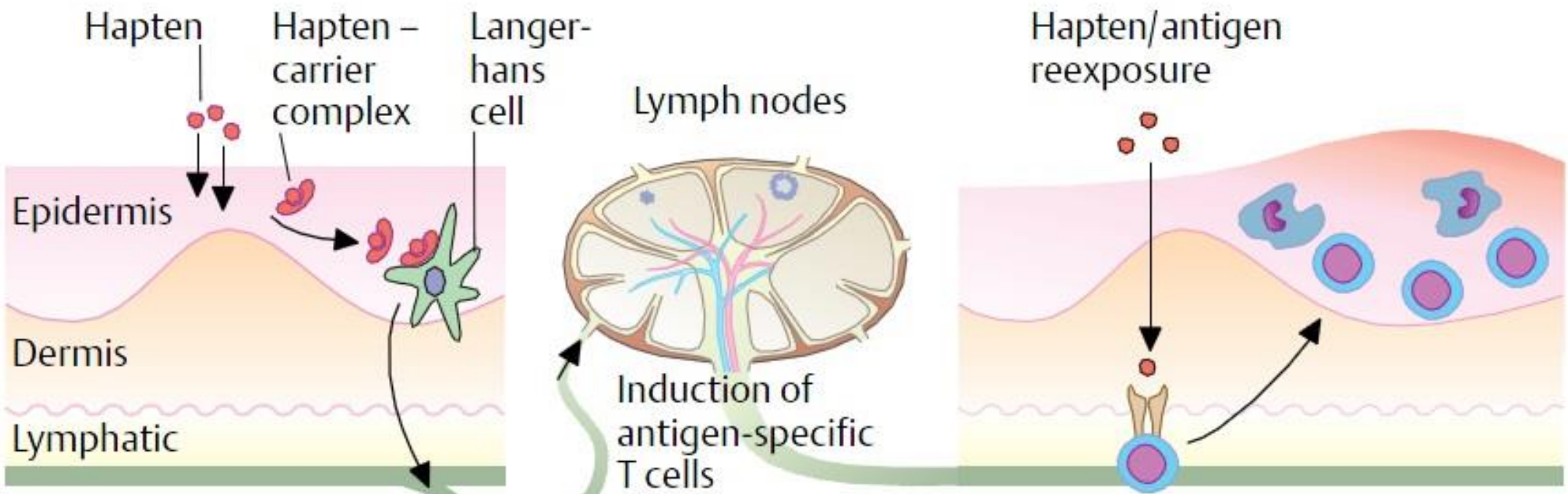
Type IV hypersensitivity reaction T cell-mediated

- Tissue injury may be due to T lymphocytes that induce inflammation or directly kill target cells.
- In most of these diseases, the major mechanism involves the activation of CD4+ helper T cells, which secrete cytokines that promote inflammation and activate leukocytes, mainly neutrophils and macrophages.
- Tc contribute to tissue injury in some diseases.

- Slow onset (1-21 days)
- Mediated by involving Th lymphocyte mechanisms (for soluble Ag) and Tc (for cell associated Ag)

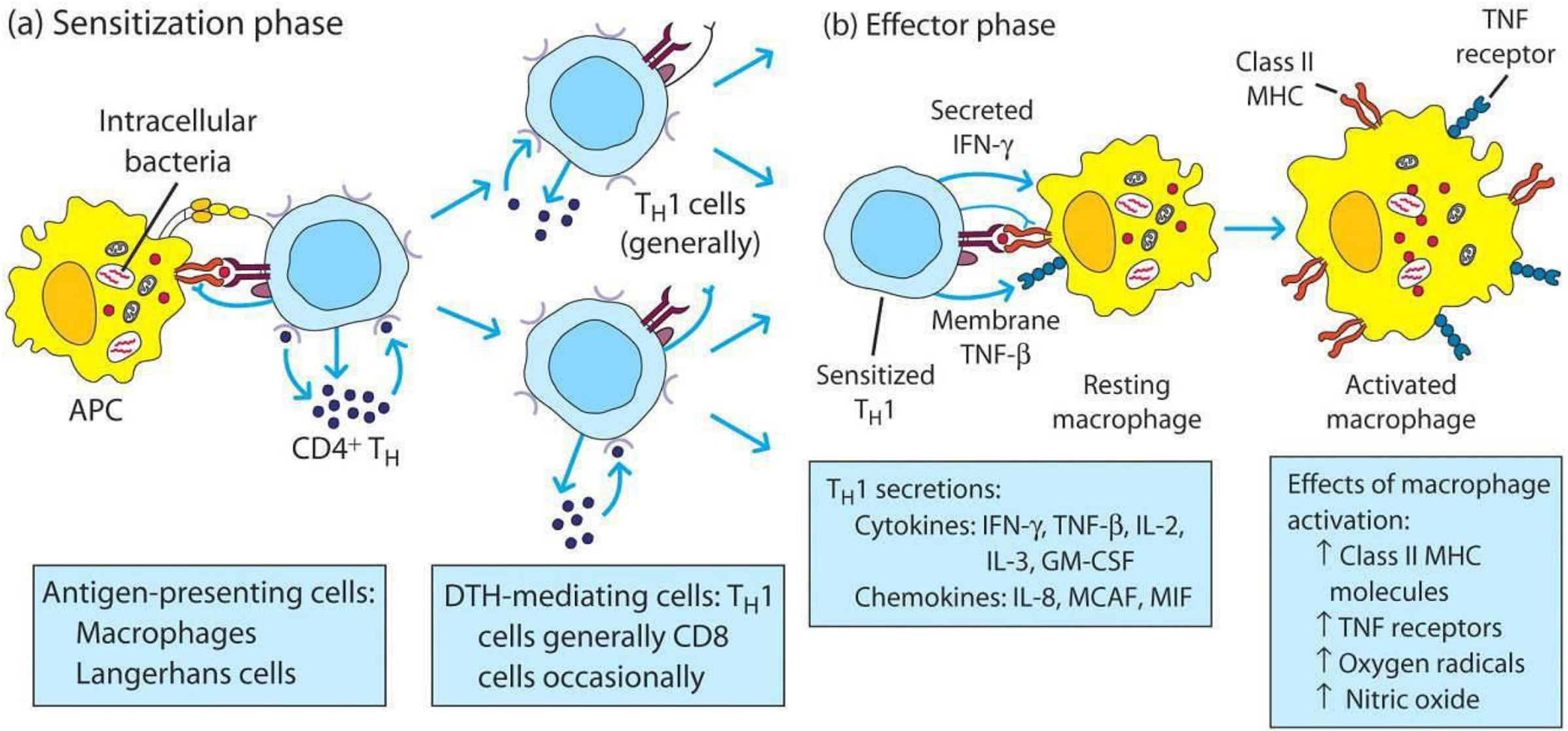
- TB skin test
- Contact dermatitis (Triggers: chemicals, cheap jewelry (Ni), antibiotics)
- Asthma eo
- Autoimmune disease (type I diabetes mellitus)

HSR type IV

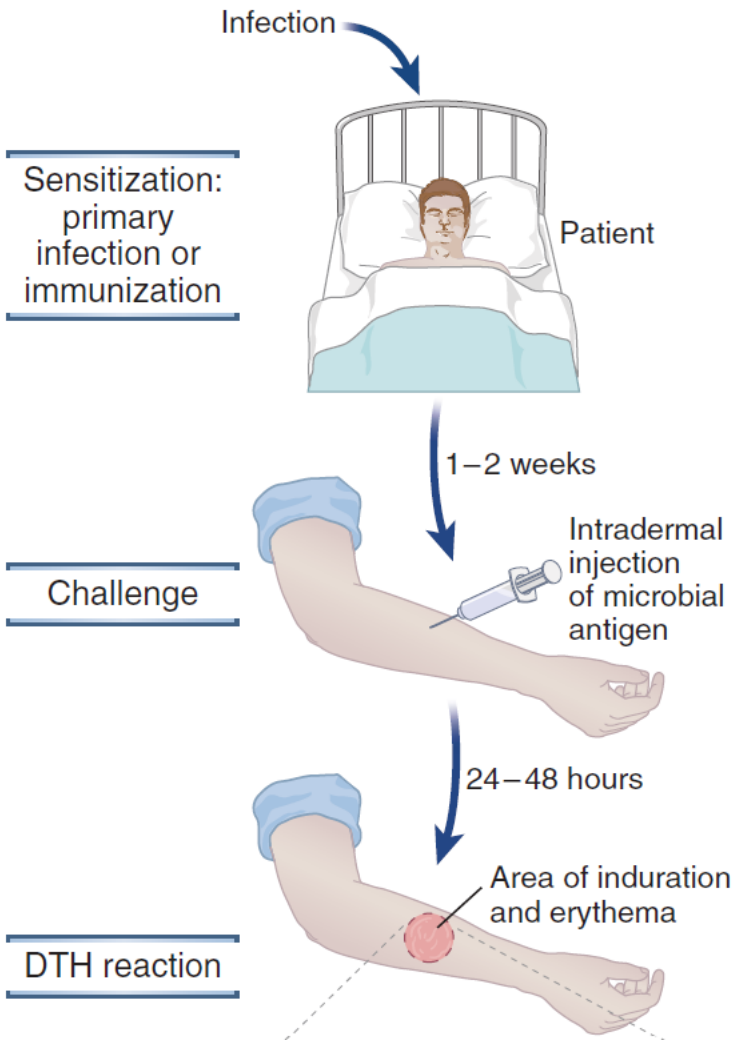


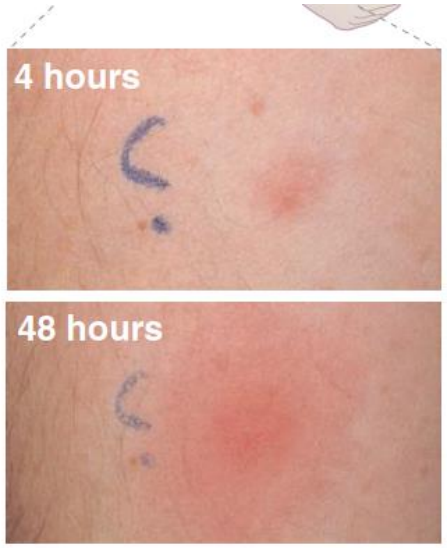
Type IV: Delayed type hypersensitivity (DTH)

HSR type IV Th1 mediated



Delayed-type hypersensitivity (DTH) reaction





- Infection or immunization (vaccination) sensitizes an individual, and subsequent challenge with an antigen from the infectious agent elicits a DTH reaction
- The reaction is manifested by induration with redness and swelling at the site of the challenge, which peaks at ~48 hours

Exemple: i.d. PPD test

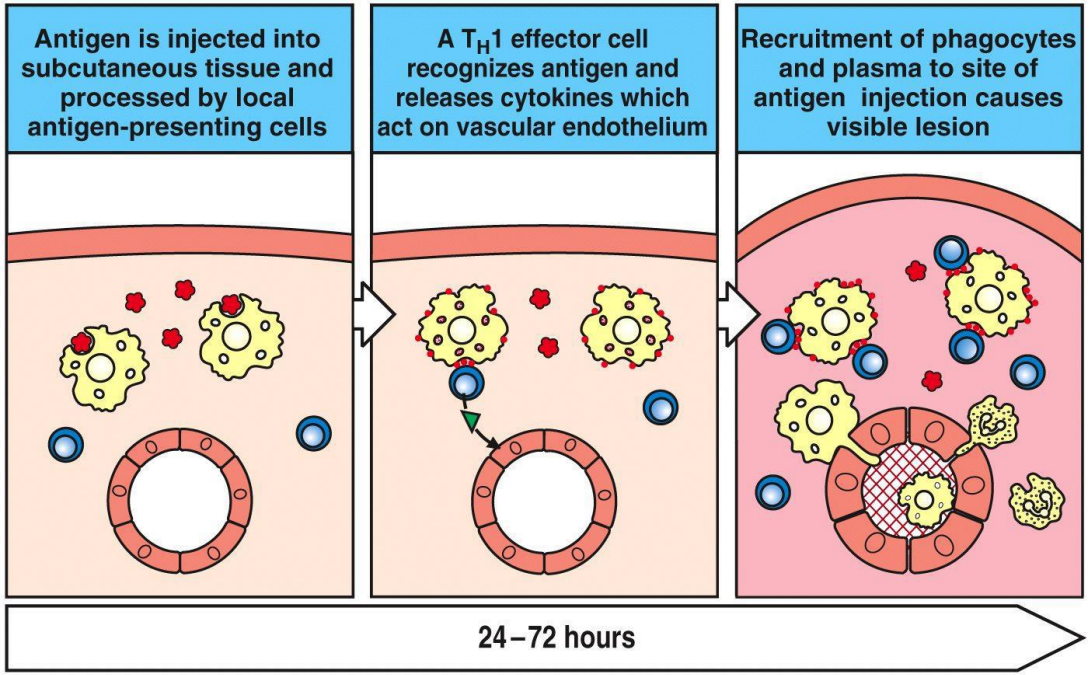


Figure 12-25 Immunobiology, 6/e. (© Garland Science 2005)

T Cell–Mediated Diseases

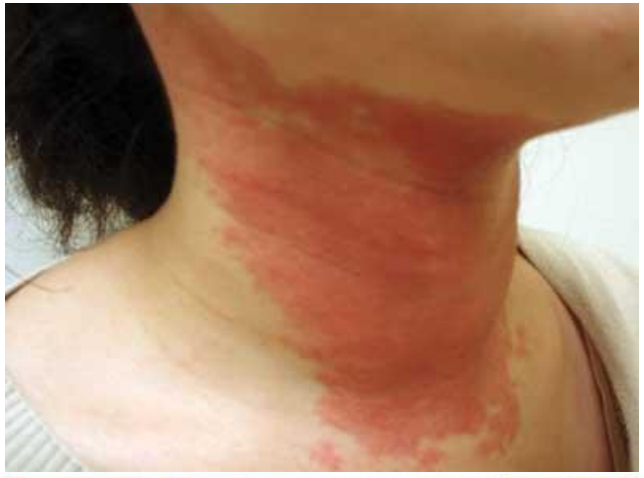
TABLE 19.4 T Cell–Mediated Diseases

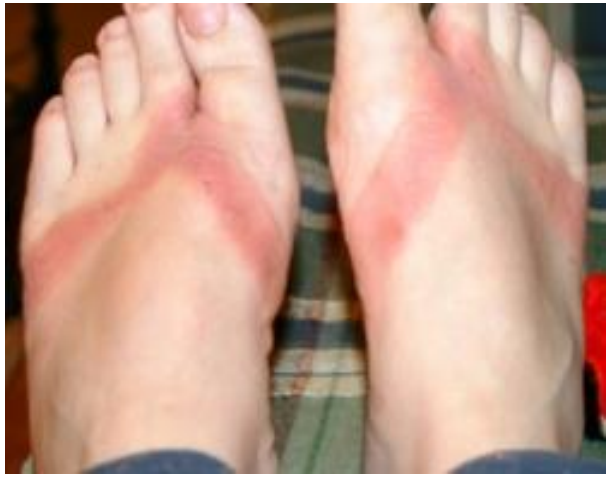
Disease	Specificity of Pathogenic T Cells	Principal Mechanisms of Tissue Injury
Rheumatoid arthritis	Collagen? Citrullinated self proteins?	Inflammation mediated by Th1 and Th17 cytokines. Role of antibodies and immune complexes?
Multiple sclerosis	Protein antigens in myelin (e.g., myelin basic protein)	Inflammation mediated by Th1 and Th17 cytokines; myelin destruction by activated macrophages
Type 1 diabetes mellitus	Antigens of pancreatic islet β cells (insulin, glutamic acid decarboxylase, others)	T cell–mediated inflammation; destruction of islet cells by CTLs
Inflammatory bowel disease	Enteric bacteria. Self antigens?	Inflammation mediated by Th1 and Th17 cytokines
Psoriasis	Unknown skin antigens	Inflammation mediated by T cell–derived cytokines

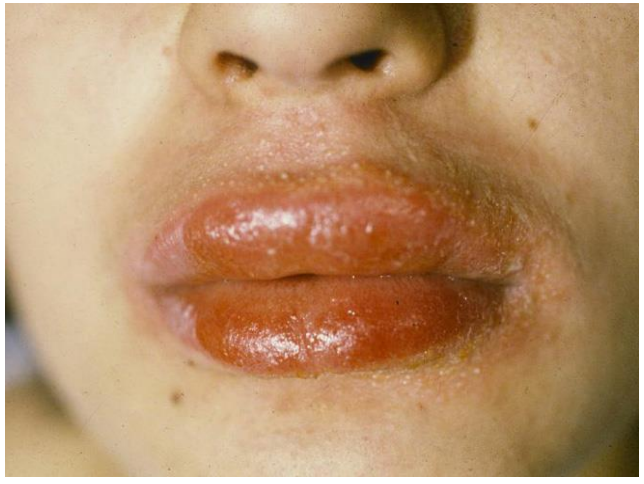
Examples of human T cell–mediated diseases are listed. In many cases, the specificity of the T cells and the mechanisms of tissue injury are inferred on the basis of the similarity with experimental animal models of the diseases. The roles of Th1 and Th17 cells have been inferred from experimental models and the presence of subset-specific cytokines in human lesions. The cytokines may be produced by cells other than $CD4^+$ T lymphocytes. Ongoing clinical trials targeting these cytokines may provide new information about the contributions of the cytokines in different diseases.

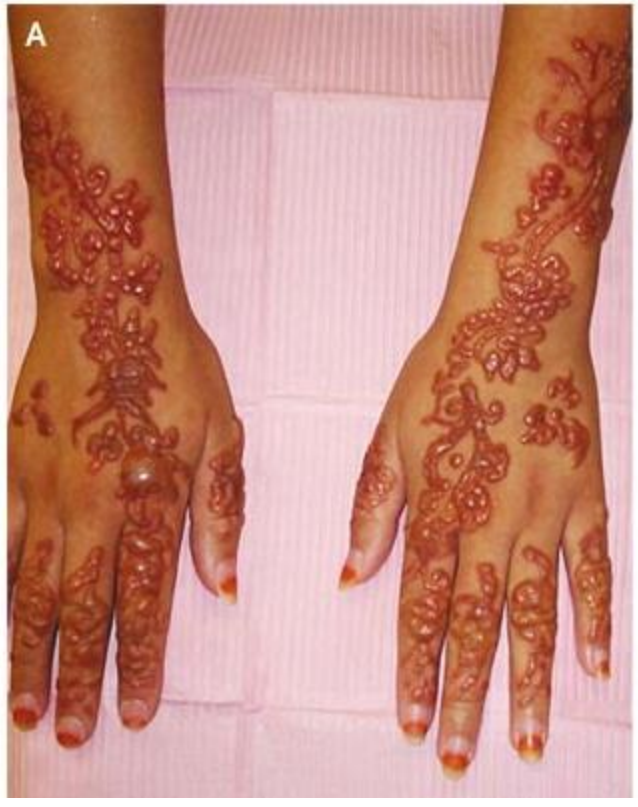
CTLs, Cytotoxic T lymphocytes.

Dermatita de contact









molecule antigenice de dimensiuni mici formează complexe cu proteine din piele

↓

fagocitarea complexelor

↓

prezentarea de către APC din piele (celule Langerhans) împreună cu HLA clasa II către LTh

↓

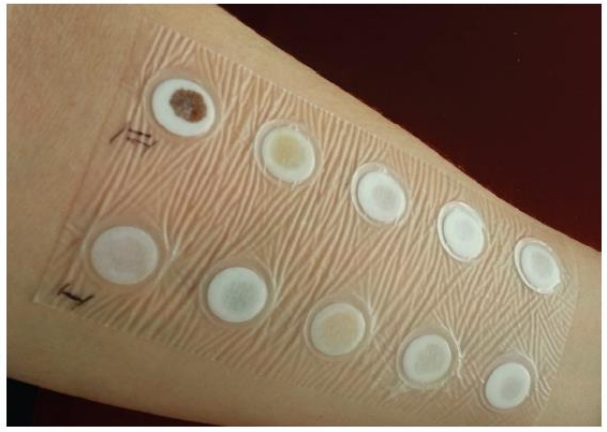
sinteză de citokine

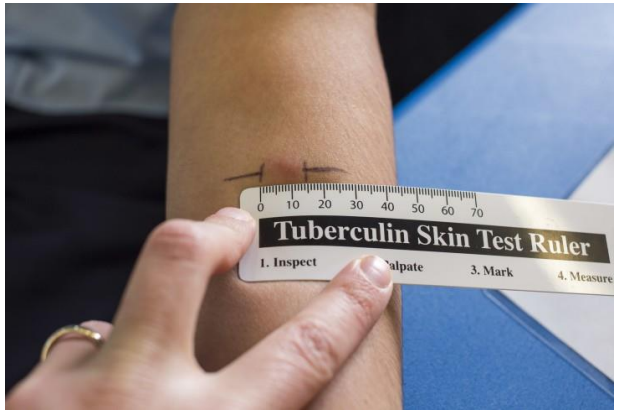
↓

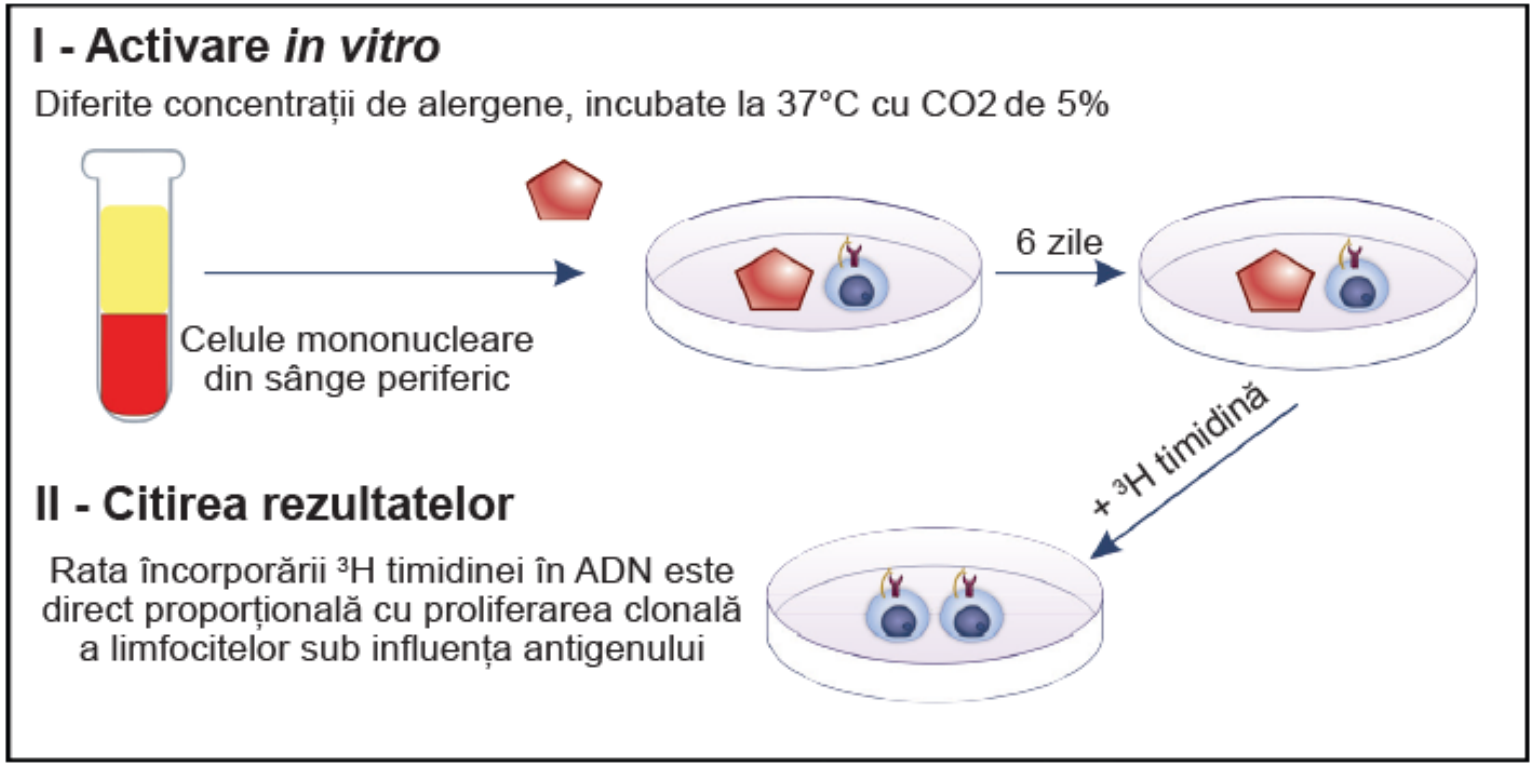
vasodilataţie cu migrarea limfocitelor şi a macrofagelor la locul reacţiei și eliberare de enzime litice

Principii de diagnostic și tratament

- **Diagnostic** - *in vivo* (test cutanat intradermic cu citire întârziată 48-72 de ore, test epicutanat *patch*) - medicamente, alergene de contact sau a infecției cu agenți microbieni (IDR la tuberculină).
- **Laborator** - testul de transformare blastică a limfocitelor (LTT) în prezența Ag inductor,







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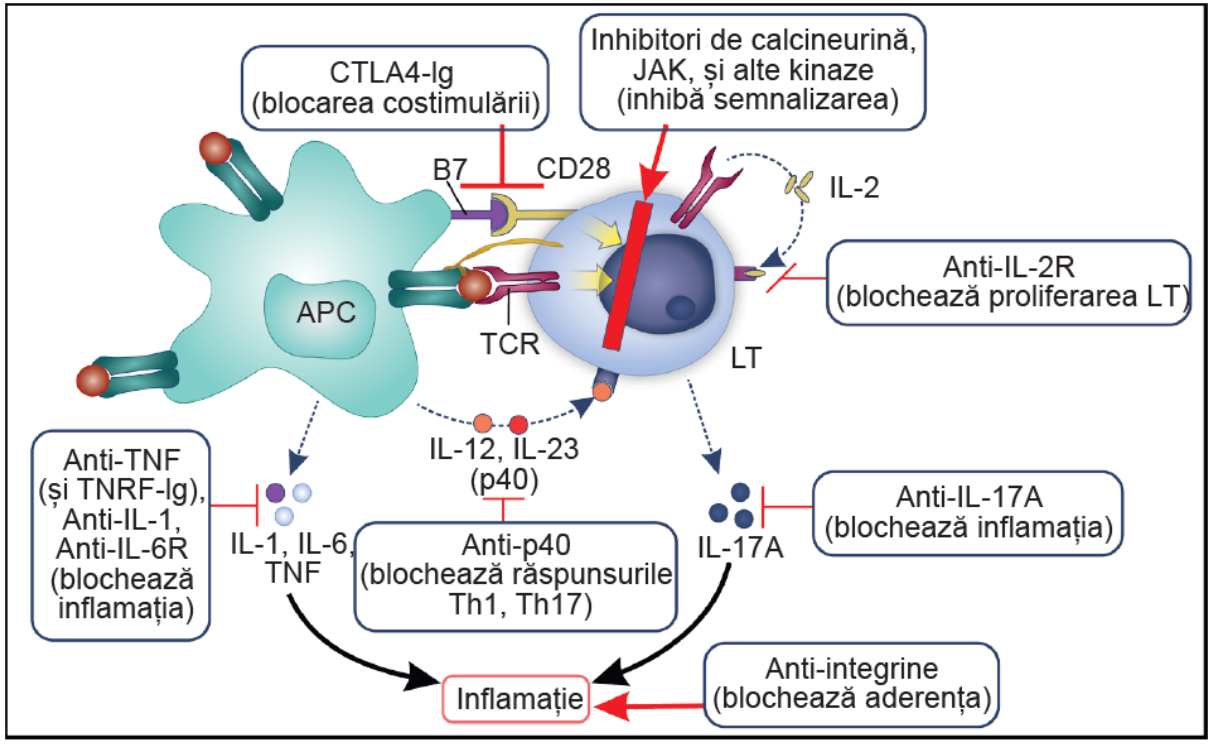
Terapiile pentru bolile inflamatorii care vizează răspunsurile LT și inflamația

- **Principiile de tratament**
- evitarea expunerii în cazul alergenilor,
- antiinflamatoare steroidiene (corticosteroizi)
- controlul diferitelor citokine proinflamatorii



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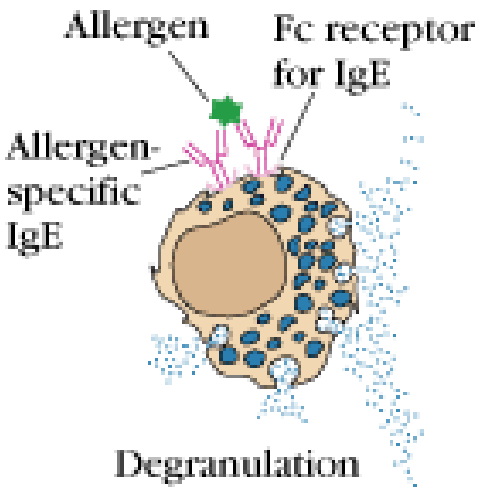
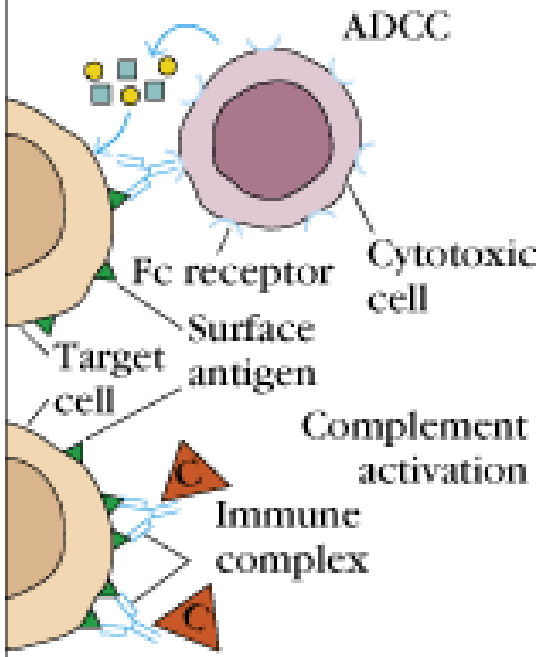
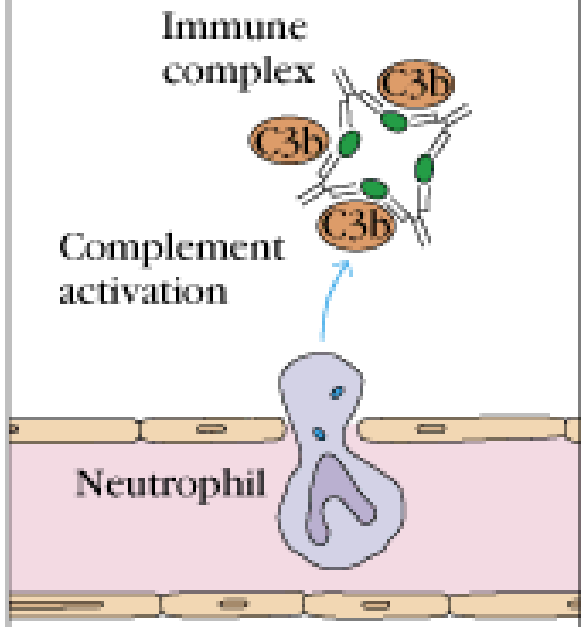
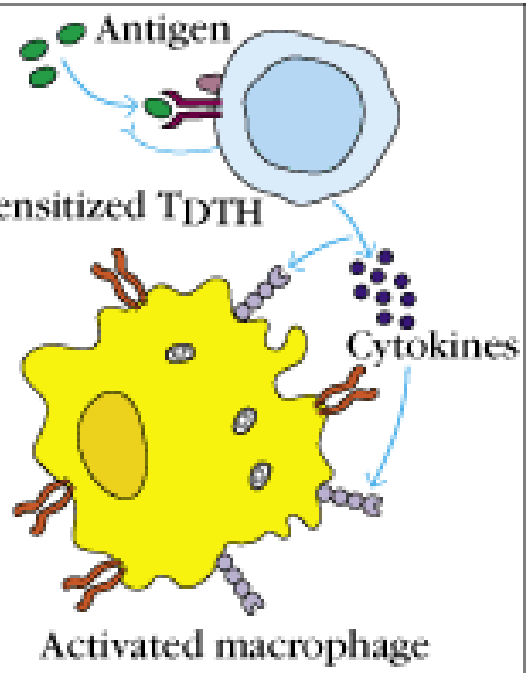
 **Type I**	 **Type II**	 **Type III**	 **Type IV**
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed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

Immunologic Tolerance and Autoimmunity

Reaction to Self - Autoimmunity

Immunologic tolerance = Unresponsiveness to an antigen that is induced by previous exposure to that antigen

Tolerance to self antigens (self-tolerance) - Fundamental property of normal immune system

Tolerogens = Antigens that induce tolerance

Immunogens = Antigens that generate immunity

Failure of self-tolerance (**Reaction to Self**) → Autoimmunity

Overview

Physiopathology of immune tolerance-related diseases influenced by several factor:

- Genetic susceptibility
- Route of exposure
- Antigen dose
- Time of exposure
- Structural characteristics of allergen/antigen
- Co-exposure with stimulators of innate immune response, such as infections or commensal bacteria

Tolerance

- Mechanisms of tolerance eliminate and inactivate lymphocytes that express high-affinity receptors for self antigens

- During generating large and diverse repertoire, some developing T and B cells may express receptors capable of recognizing normal molecules in that individual (self antigens)

- Tolerance - antigen specific, from recognition of antigens by individual clones of lymphocytes

Self-tolerance

Self-tolerance may be induced in immature self-reactive lymphocytes in generative lymphoid organs (central tolerance) or in mature lymphocytes in peripheral sites (peripheral tolerance)

Central tolerance - Mature naive lymphocytes becomes incapable of responding to self antigens expressed in thymus for T cells and bone marrow for B lymphocytes

Self-reactive lymphocytes complete their maturation → **Peripheral tolerance**

Central Tolerance occurs during stage in maturation of lymphocytes when encounter with antigen may lead to cell death or replacement of self-reactive antigen receptor with one that is not self-reactive

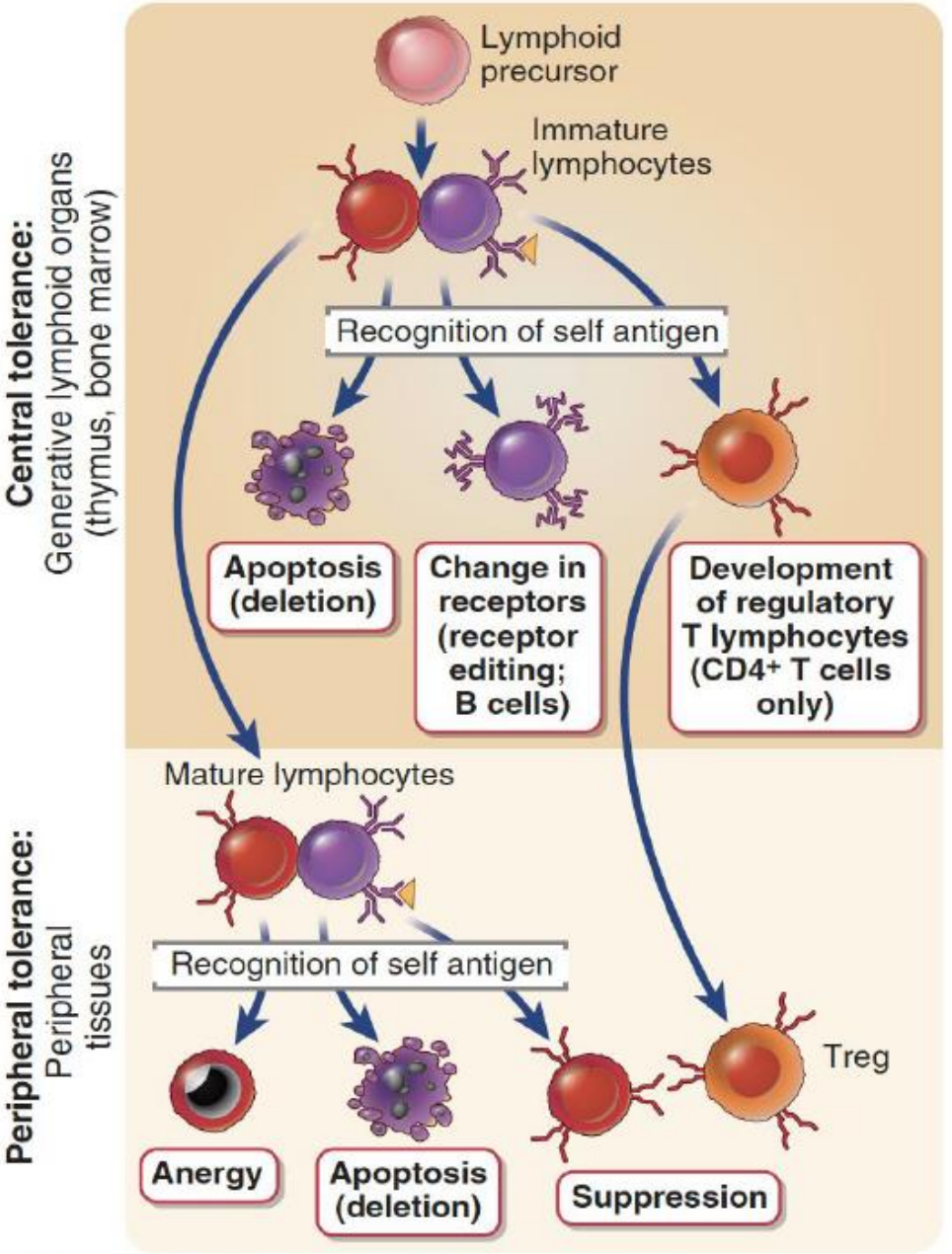
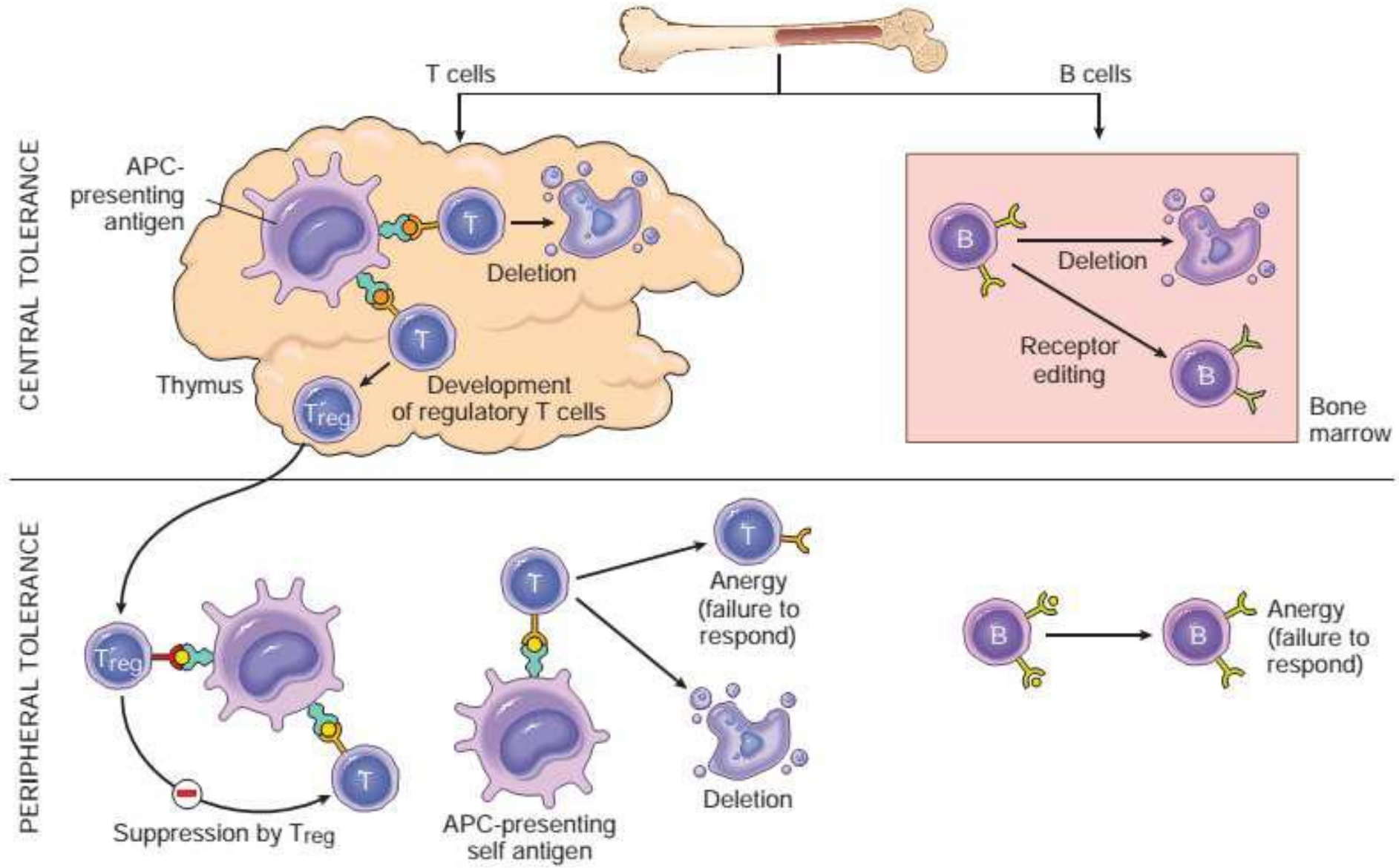


FIGURE 15.1 Central and peripheral tolerance to self antigens.


T cells
B cells
CENTRAL TOLERANCE
APC-presenting antigen
T
Deletion
T
Thymus
Treg
Development of regulatory T cells
B
Deletion
Receptor editing
B
Bone marrow
PERIPHERAL TOLERANCE
Treg
T
Suppression by Treg
T
Anergy (failure to respond)
Deletion
APC-presenting self antigen
B
B
Anergy (failure to respond)

- **Mature lymphocytes that recognize self antigens in peripheral tissues become incapable of activation by re-exposure to that antigen or die by apoptosis**

Important mechanism for the induction of peripheral tolerance = Antigen recognition **without costimulation or "second signals"**

- **Peripheral tolerance maintained by regulatory T cells (Tregs) that actively suppress activation of lymphocytes**

Central T Cell Tolerance

During their maturation in thymus, many immature T cells that recognize antigens with high avidity **die**, and some of surviving cells in the CD4+ lineage **develop into Tregs**

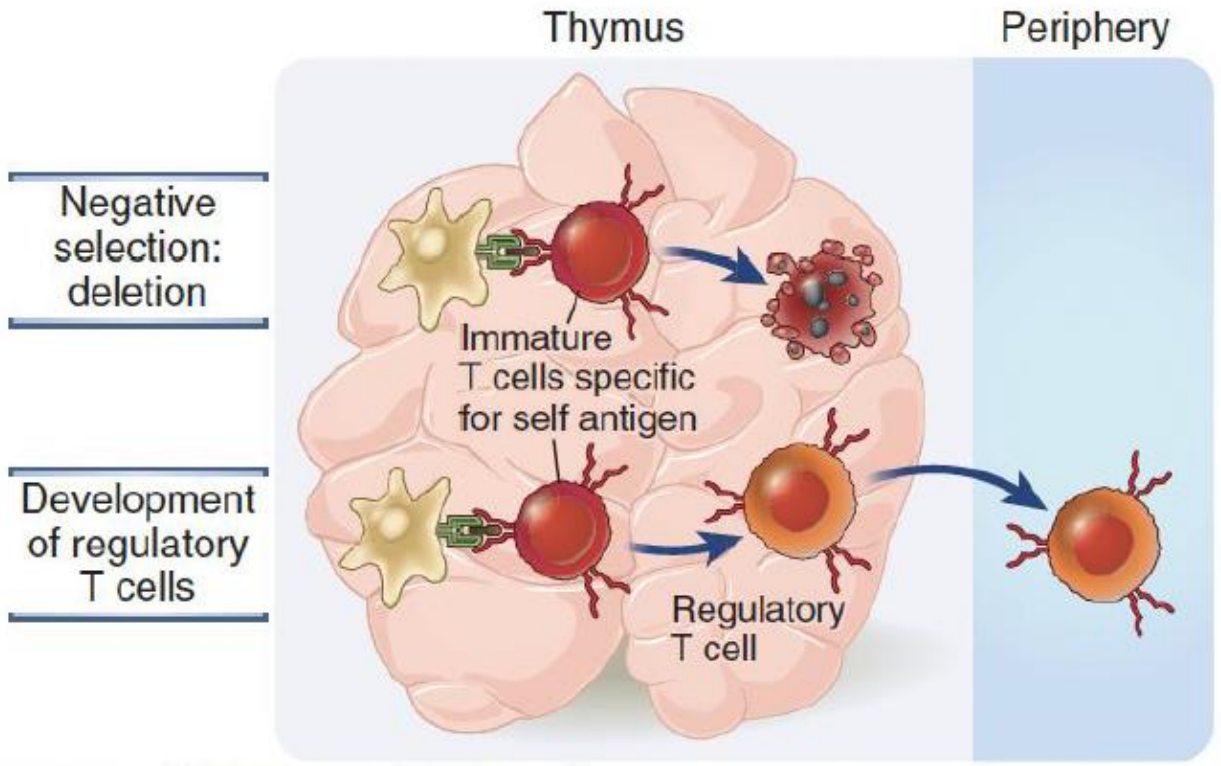
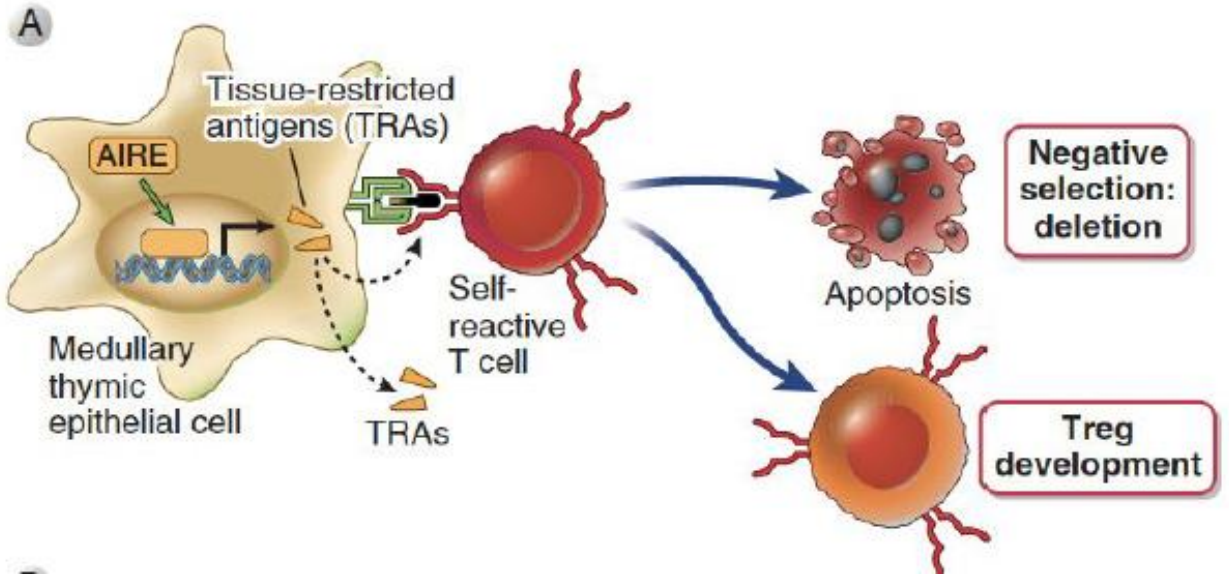


FIGURE 15.2 Central T cell tolerance.

Central T Cell Tolerance

● Thymus has special mechanism for expressing many protein antigens expressed in different peripheral tissues, produced in medullary thymic epithelial cells (**MTECs**) under the control of the autoimmune regulator (**AIRE**) protein, immature T cells specific for these antigens can be deleted

● **Mutations in the AIRE gene** are the cause of a multi-organ autoimmune disease, **autoimmune polyendocrine syndrome type 1 (APS1)** characterized by antibody- and lymphocyte-mediated injury to multiple endocrine organs; parathyroids, adrenals, and pancreatic islets



Central T Cell Tolerance

- In the absence of functional **AIRE**, these antigens are not displayed in the thymus, and T cells specific for the antigens escape deletion, mature, and enter the periphery → attack target tissues

- Patients with AIRE mutations also make neutralizing **autoantibodies against their own IL-17**

- **Deficiency of IL-17** → patients susceptible to mucocutaneous candidiasis

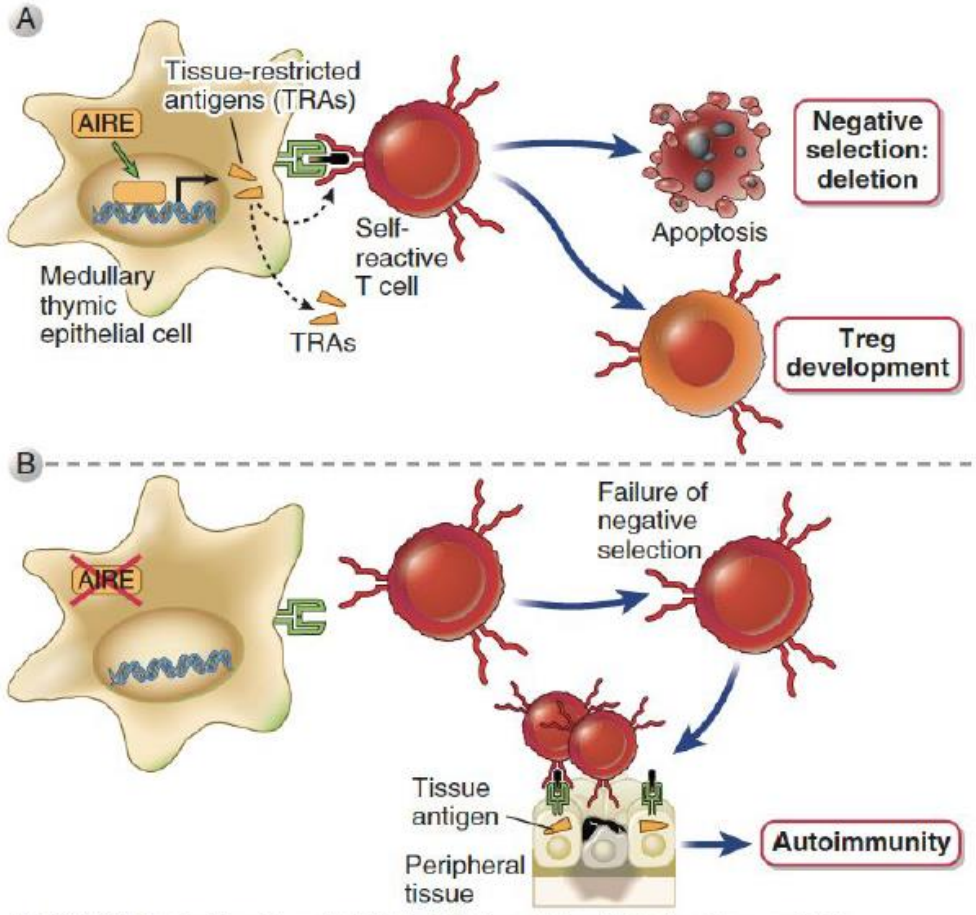


FIGURE 15.3 The function of AIRE in deletion of T cells in the thymus. A, The

Central T Cell Tolerance

- Regulatory cells leave the thymus and inhibit responses against self antigens in the periphery

- Determination of **deletion** **OR** **development of Tregs**

- **Affinity** of antigen recognition

- **Types of antigen presenting cells** (APCs) presenting antigen

- Availability of **cytokines** in thymus

Peripheral T Cell Tolerance

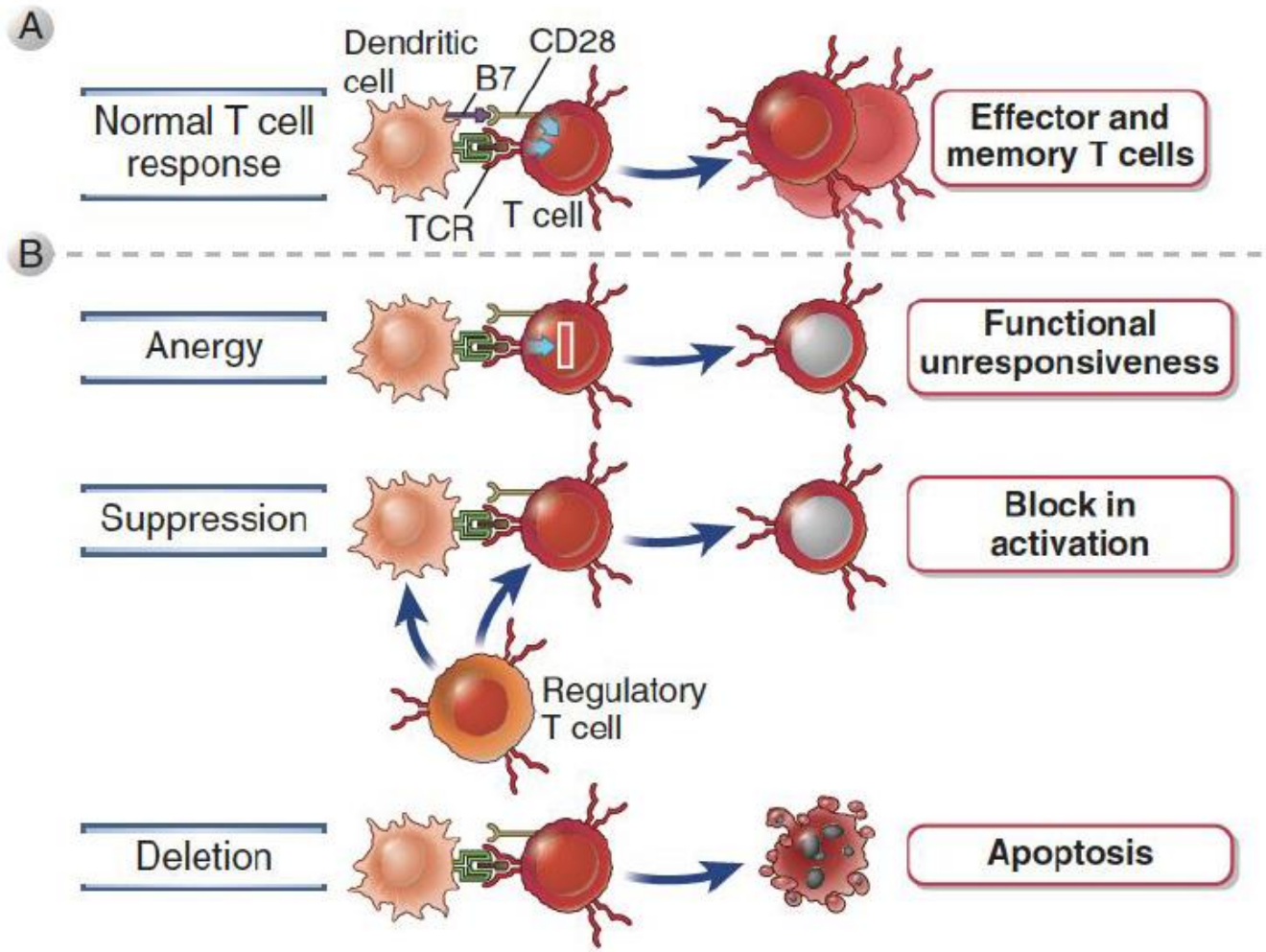


FIGURE 15.4 Mechanisms of peripheral T cell tolerance.

Peripheral T Cell Tolerance

Anergy (Functional Unresponsiveness)

- Exposure of mature CD4+ T cells to antigen in **absence of costimulation or innate immunity** may make the cells incapable of responding to that antigen

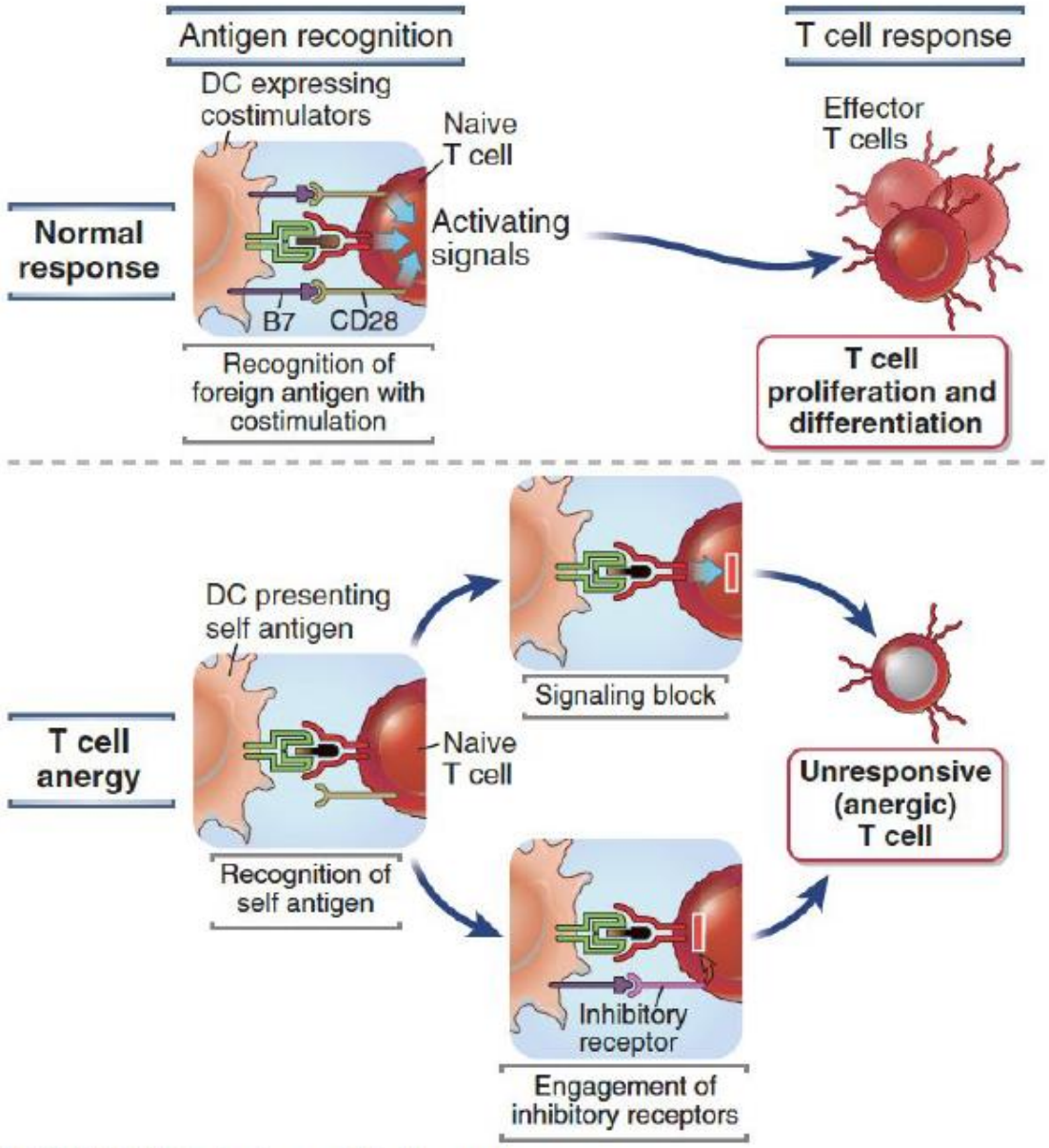


FIGURE 15.5 Mechanisms of T cell anergy.

Peripheral T Cell Tolerance

Mechanisms induce and maintain anergic state

- **TCR-induced signal transduction is blocked** in anergic cells
- Self antigen recognition may **activate cellular ubiquitin ligases** → ubiquitinate TCR-associated proteins and target them for proteolytic degradation in proteasomes or lysosomes
- T cells recognize self antigens, they engage **inhibitory receptors** of CD28 family, whose function is to **terminate T cell responses**

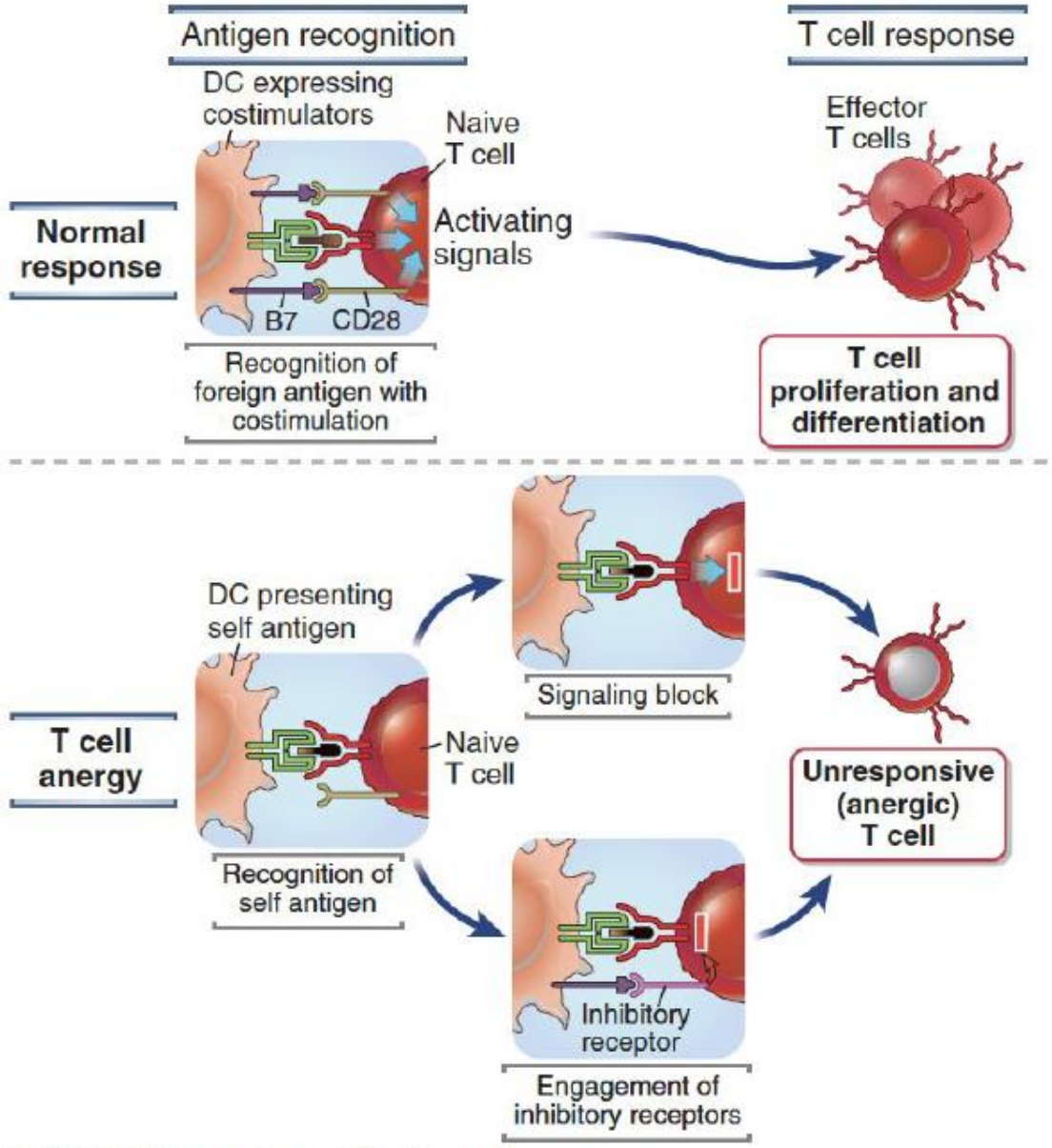


FIGURE 15.5 Mechanisms of T cell anergy.

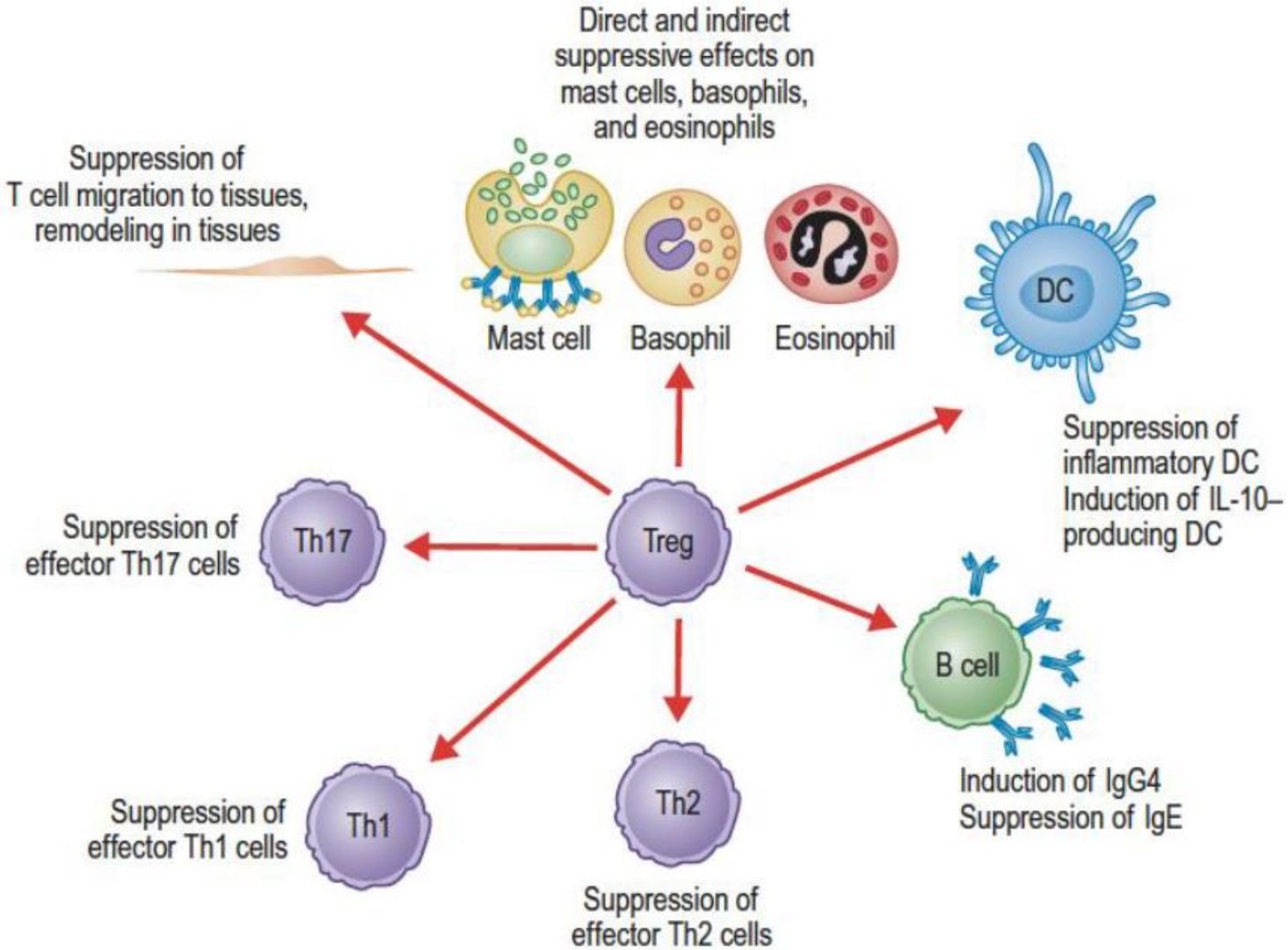


Fig. 4.7 Immune deviation toward Treg cell response is an essential step in allergen immunotherapy and natural allergen exposure of nonallergic individuals.

Mubeccel Akdis, et al. Middleton's Allergy. 9th Edition;2020:44-64.e1.

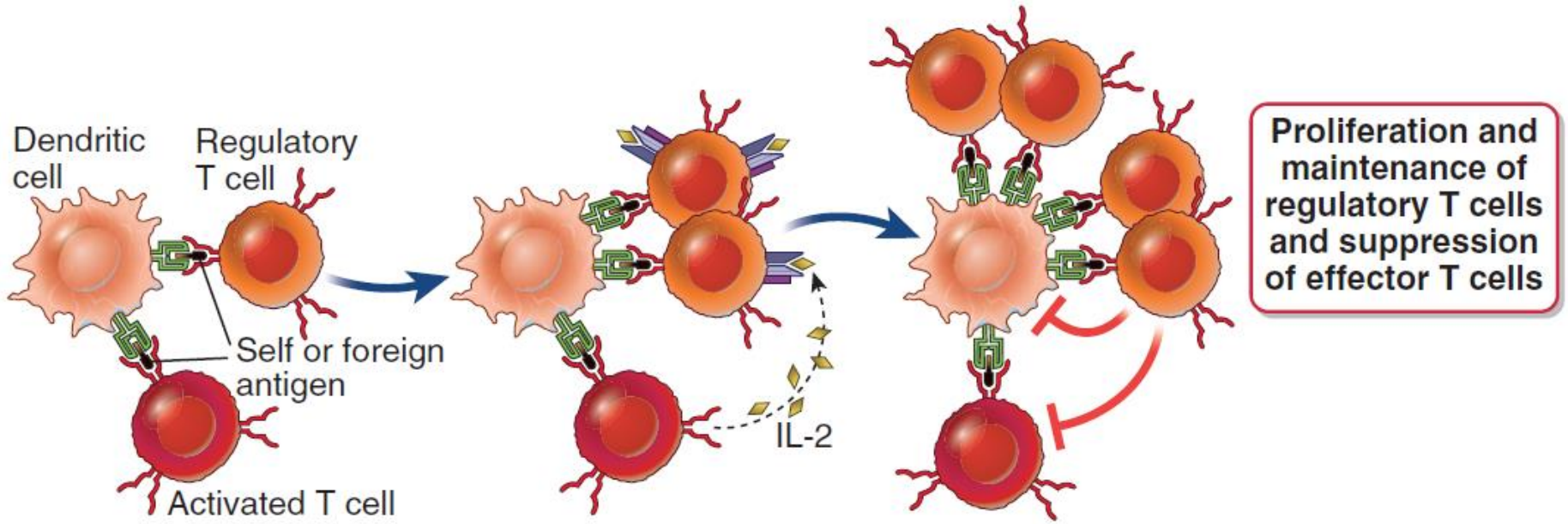


FIGURE 15.9 Role of interleukin-2 in the maintenance of regulatory T cells. IL-2 produced by conventional T cells responding to self or foreign antigens acts on Tregs recognizing the antigen on APCs and promotes the survival and function of the Tregs, enabling them to control the responses of the conventional T cells. *IL-2,* Interleukin-2.

B Lymphocyte Tolerance

- Maintaining unresponsiveness to thymus-independent self antigens, such as polysaccharides and lipids
- Preventing antibody responses to protein antigens

Central B Cell Tolerance

Immature B lymphocytes that recognize self antigens in the bone marrow with high affinity change their specificity or are deleted

Receptor editing

B cells reactivate their RAG1 and RAG2 genes and initiate new round of VJ recombination in the Ig kappa light chain gene locus

Previously rearranged V kappa J kappa exon in self-reactive immature B cell is deleted, and new Ig light chain is expressed, thus creating BCR with new specificity

Deletion

Anergy

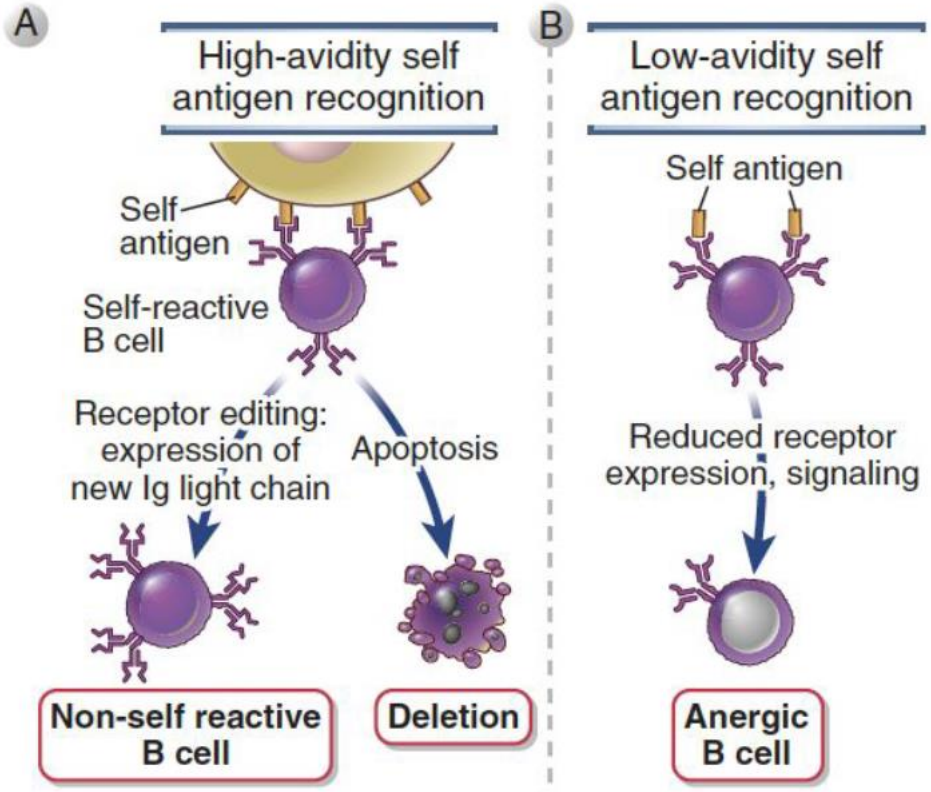


FIGURE 15.11 Central tolerance in B cells. A,

Peripheral B Cell Tolerance

Mature B lymphocytes that recognize self antigens in peripheral tissues in absence of specific helper T cells → functionally unresponsive or → apoptosis

- Signals from helper T cells may be absent if these T cells are **deleted** or **anergic** or if the self antigens are non-protein antigens
- As in T cells, antigen recognition **without additional stimuli** results in tolerance

Anergy and deletion

- Some self-reactive B cells that are repeatedly stimulated by self antigens become unresponsive
- Require higher than normal levels of the growth factor BAFF for survival
- Have shortened life span
- B cells that bind with high avidity to self antigens in periphery may also undergo apoptotic death by **mitochondrial pathway**

Signaling by inhibitory receptors

Immunoreceptor tyrosine-based activation motifs (ITIMs) in cytoplasmic tail of CD22 are phosphorylated by Lyn, and this inhibitory receptor then recruits SHP-1, thus attenuating B cell receptor signaling

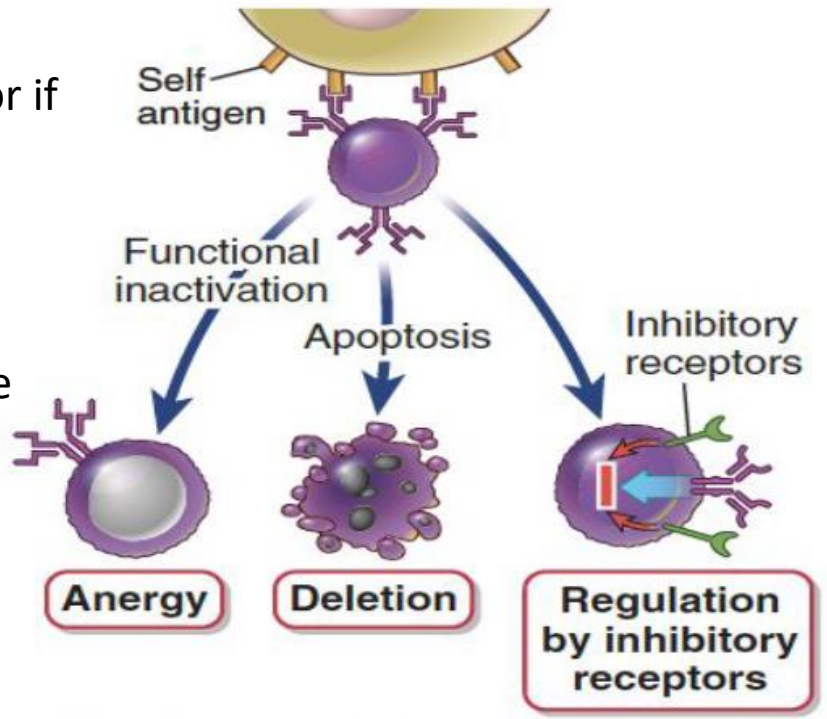


FIGURE 15.12 Peripheral tolerance in B cells.

Autoimmunity

Immune reactions against self antigens

Bolile autoimune

Definition

Autoimmune diseases are a heterogeneous group of conditions characterised by the presence of circulating antibodies against their own constituents (self structures).

It is not known why the body loses the ability to distinguish self - non-self

Clinical significance

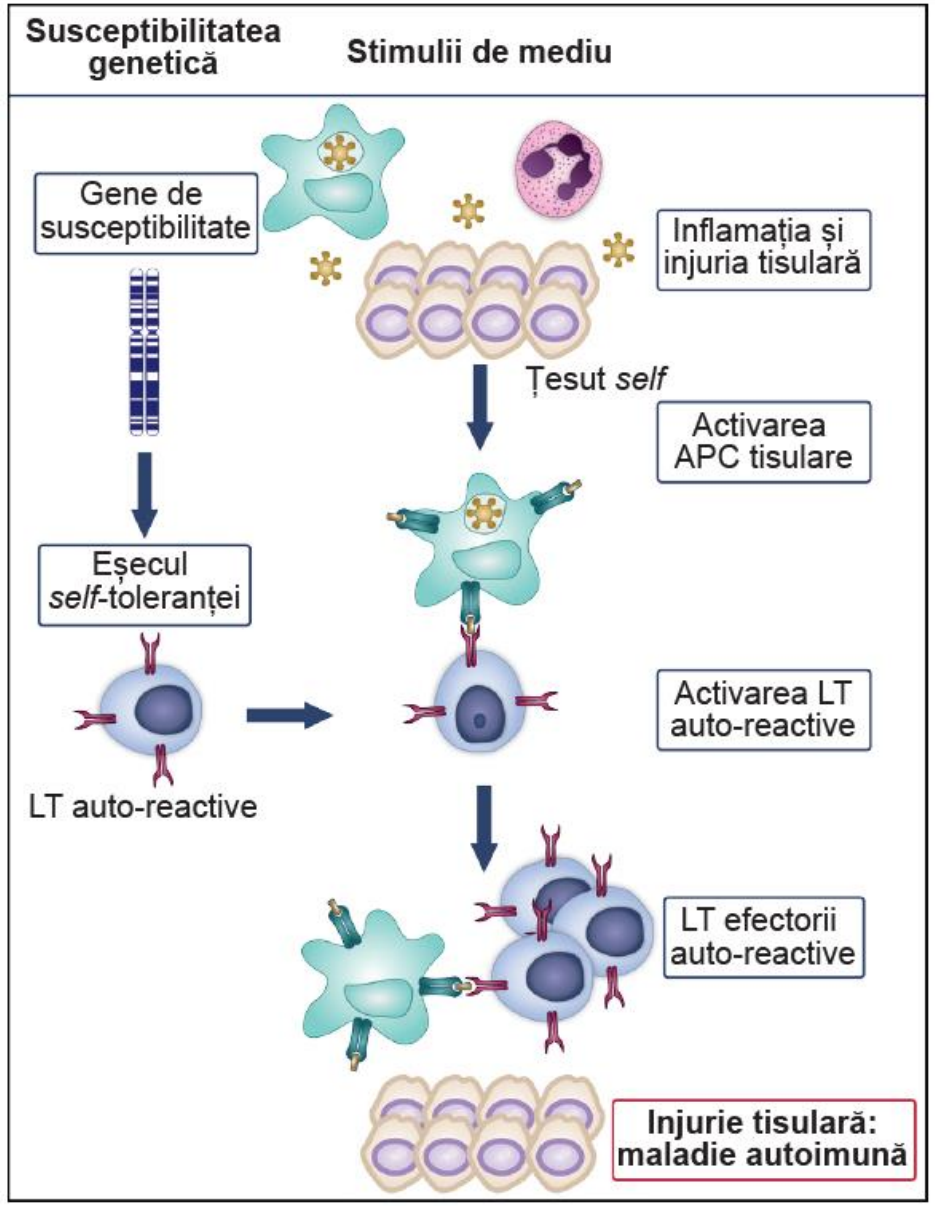
- Autoimmune disease – specific spectrum of auto-antibodies
- 2 types immune response:
- organ specific →organ autoimmune disease (e.g. diabetes),
- non-organ specific → systemic autoimmune disease (e.g. scleroderma)

Pathogenesis of Autoimmunity

- General Features of Autoimmune Disease:

• Autoimmune diseases tend to be chronic, sometimes with relapses and remissions, and the damage is often progressive

• The clinical and pathologic manifestations of an autoimmune disease are determined by the nature of the underlying immune response



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Mechanisms related to autoimmunity

- Defective tolerance or regulation
- Abnormal display of self antigens
- Inflammation or an initial innate immune response
- Antigen Mimicry
- Alteration of Normal Proteins
- Release of Sequestered antigens
- Epitope spreading
- Failure of Regulatory T Cells

Pathogenic mechanisms of AutoAb production

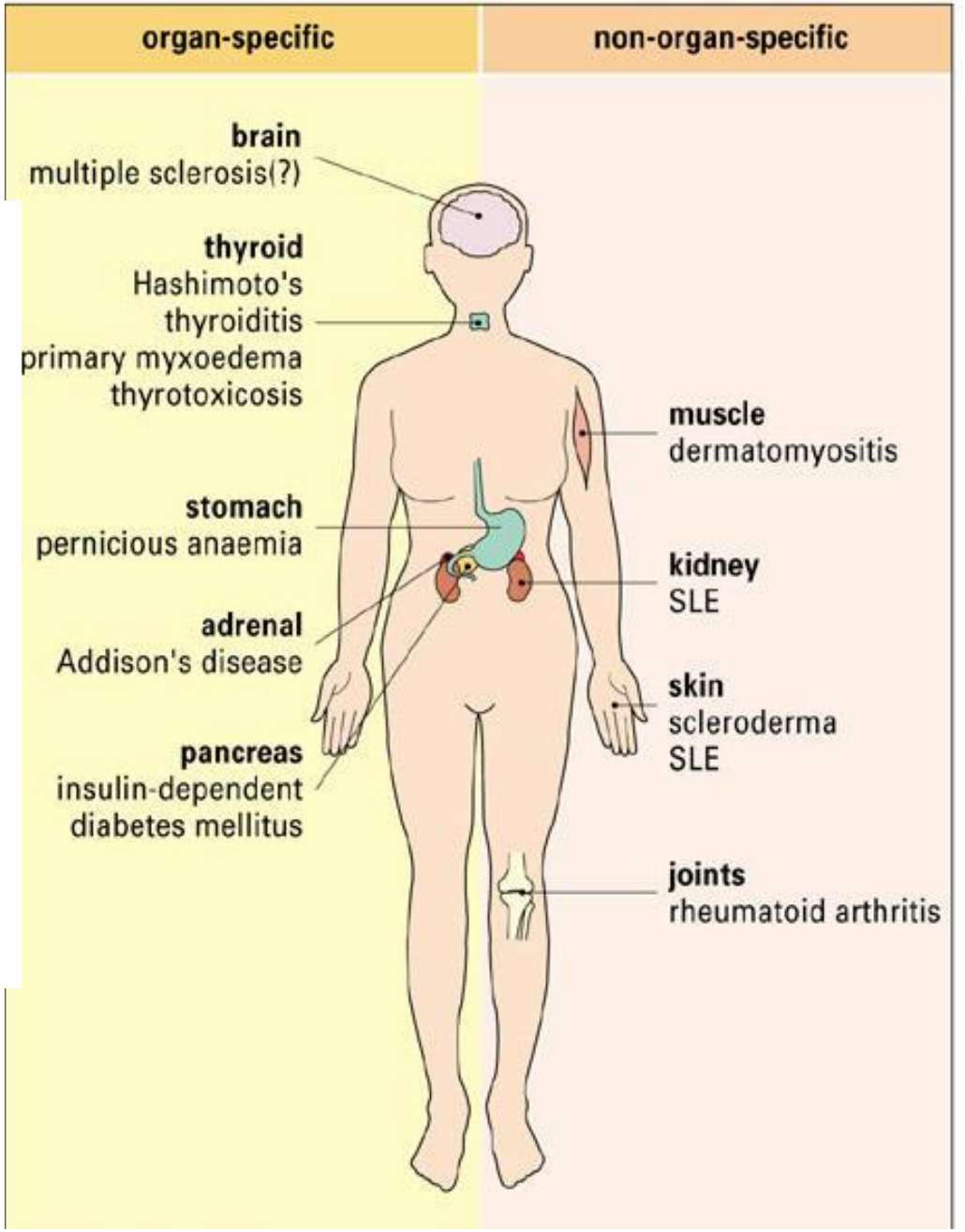
Bazele fiziopatologice ale mecanismelor reacțiilor autoimune sunt RHS de tip II (Ag *self* - auto-Ac)

<table>
<tr><td rowspan="2">Abnormalities in autoantibody synthesis</td><td>Alterations of central tolerance</td><td>Self-reactive LT or LB (positive/negative selection defects)</td></tr>
<tr><td>Alterations of peripheric tolerance</td><td>LT (defects of apoptosis and survival of autoreactive LT)

LB (defects of regulatory mechanisms)</td></tr>
<tr><td rowspan="3">Abnormalities of Ag</td><td colspan="2"><u>Changes (alteration) in protein structure:</u>
Altered self theory by physical, chemical, tumor factors (DAMPs)</td></tr>
<tr><td colspan="2"><u>Molecular mimicry</u>
antigenic similarity between exogenous Ag and self components</td></tr>
<tr><td colspan="2"><u>Superantigens</u> stafilococice în PR</td></tr>
</table>

Examples of autoimmune diseases

Organ-Specific	Systemic
Diseases Mediated by Antibodies	
Autoimmune hemolytic anemia	Systemic lupus erythematosus
Autoimmune thrombocytopenia	
Autoimmune atrophic gastritis of pernicious anemia	
Myasthenia gravis	
Graves disease	
Goodpasture syndrome	
Diseases Mediated by T Cells*	
Type 1 diabetes mellitus	Rheumatoid arthritis
Multiple sclerosis	Systemic sclerosis (scleroderma)† Sjögren syndrome†
Diseases Postulated to Be Autoimmune	
Inflammatory bowel diseases (Crohn disease, ulcerative colitis)‡	
Primary biliary cirrhosis†	Polyarteritis nodosa†
Autoimmune (chronic active) hepatitis	Inflammatory myopathies†



Association of MHC Alleles With Autoimmunity

TABLE 15.3 Association of HLA Alleles With Autoimmune Disease

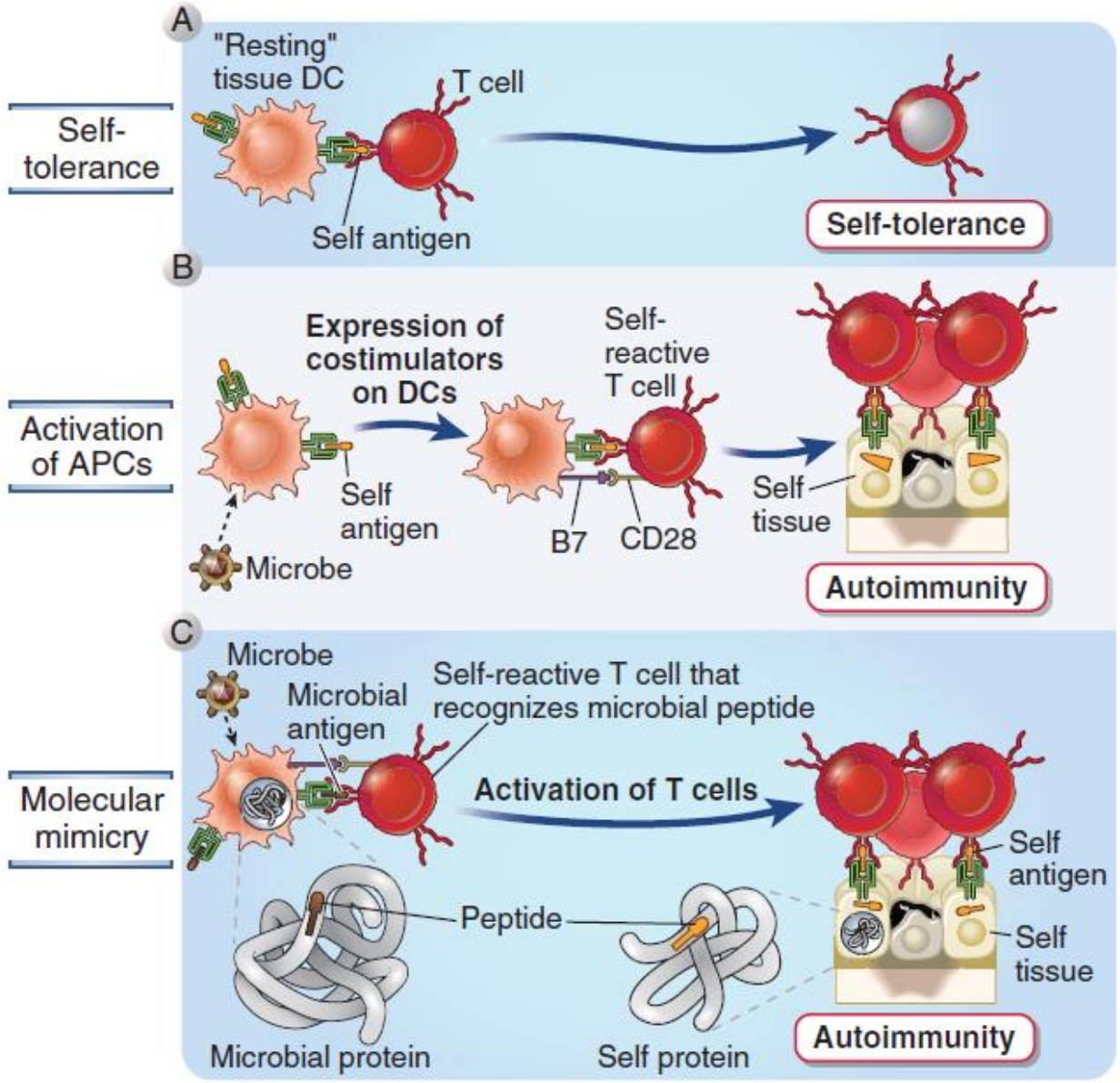
Disease	HLA Allele	Odds Ratio*
RA (anti-CCP Ab positive)†	*DRB1, 1 SE* allele‡	4
	DRB1, 2 SE alleles	12
T1D	*DRB1*0301-DQA1*0501-DQB1*0201* haplotype	4
	*DRB1*0401-DQA1*0301-DQB1*0302* haplotype	8
	*DRB1*0301/0401* heterozygotes	35
Multiple sclerosis	*DRB1*1501*	3
SLE	*DRB1*0301*	2
	*DRB1*1501*	1.3
AS	*B*27* (mainly *B*2705* and *B*2702*)	100–200
Celiac disease	*DQA1*0501-DQB1*0201* haplotype	7

Role of infections in the development of autoimmunity

A, Normally, encounter of a mature self-reactive T cell with a self antigen presented by a costimulator-deficient resting tissue APC results in peripheral tolerance by anergy. (Other possible mechanisms of self-tolerance are not shown)

B, Microbes may activate the APCs to express costimulators, and when these APCs present self antigens, the self-reactive T cells are activated rather than rendered tolerant.

C, Some microbial antigens may cross-react with self antigens (molecular mimicry). Therefore, immune responses initiated by the microbes may activate T cells specific for self antigens.



Autoantibodies and their association with different diseases

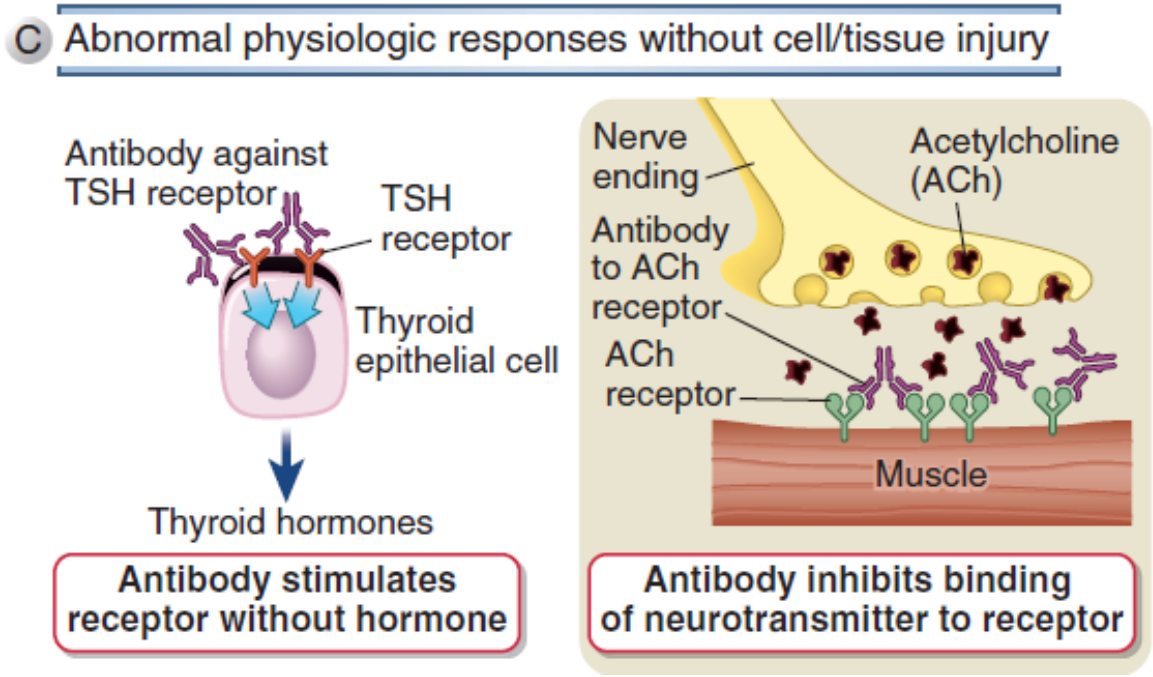
Disease	Specificity of Autoantibody	% Positive	Association with Specific Disease Features
Systemic lupus erythematosus (SLE)	Double-stranded DNA	40-60	Nephritis; specific for SLE
	U1-RNP	30-40	
	Smith (Sm) antigen (core protein of small RNP particles)	20-30	Specific for SLE
	Ro (SS-A)/La (SS-B) nucleoproteins	30-50	Congenital heart block; neonatal lupus
	Phospholipid-protein complexes (anti-PL)	30-40	Antiphospholipid syndrome (in ~10% of SLE patients)
	Multiple nuclear antigens ("generic ANAs")	95-100	Found in other autoimmune diseases, not specific.
Systemic sclerosis	DNA topoisomerase 1	30-70	Diffuse skin disease, lung disease; specific for systemic sclerosis
	Centromeric proteins (CENPs) A, B, C	20-40	Limited skin disease, ischemic digital loss, pulmonary hypertension
	RNA polymerase III	15-20	Acute onset, scleroderma renal crisis, cancer
Sjögren syndrome	Ro/SS-A La/SS-B	70-95	
Autoimmune myositis	Histidyl aminoacyl-tRNA synthetase, Jo1	25	Interstitial lung disease, Raynaud phenomenon
	Mi-2 nuclear antigen	5-10	Dermatomyositis, skin rash
	MDA5 (cytoplasmic receptor for viral RNA)	20-35 (Japanese)	Vascular skin lesions, interstitial lung disease
	TIF1γ nuclear protein	15-20	Dermatomyositis, cancer
Rheumatoid arthritis	CCP (cyclic citrullinated peptides); various citrullinated proteins	60-80	Specific for rheumatoid arthritis
	Rheumatoid factor (not specific)	60-70	

Autoantibodies and their association with different diseases

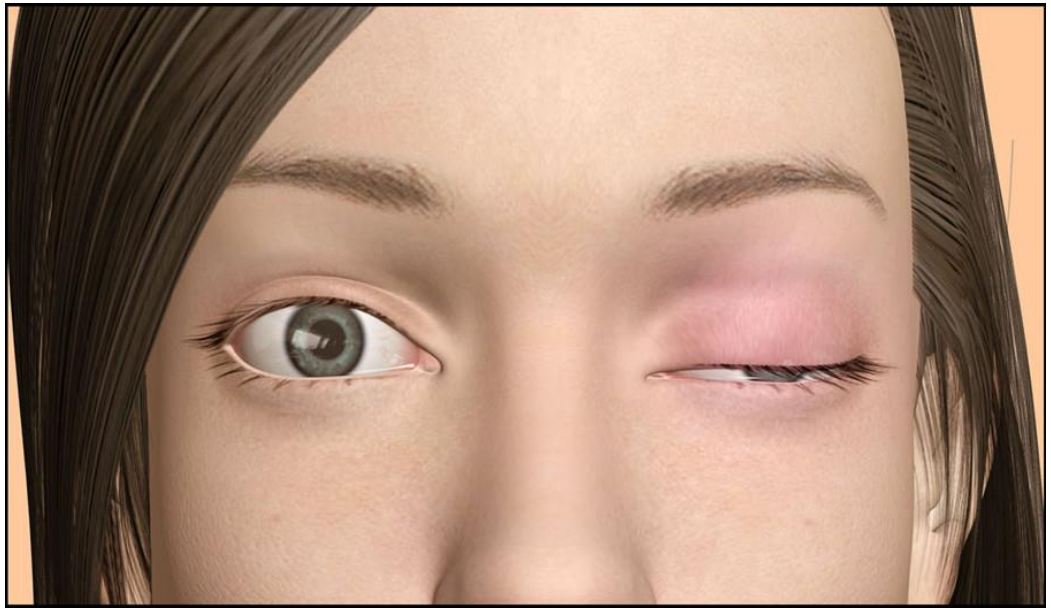
Antibodies	Prevalence (%)	Related autoimmune diseases
Rheumatoid factors (RF)	40–50	Hypergammaglobulinemia
Cryoglobulins	10–15	Lymphoma development and death
Anti-centromere antibodies (ACA)	4–17	Systemic sclerosis
Anti-mitochondrial antibodies (AMA)	5–6.5	Primary biliary cirrhosis
Anti-cyclic citrullinated peptide antibodies (anti-CCP)	7–10	Articular manifestations
Anti-smooth muscle antibodies (ASMA)	6.5–62	Autoimmune hepatitis

Autoantibodies and their association with different diseases

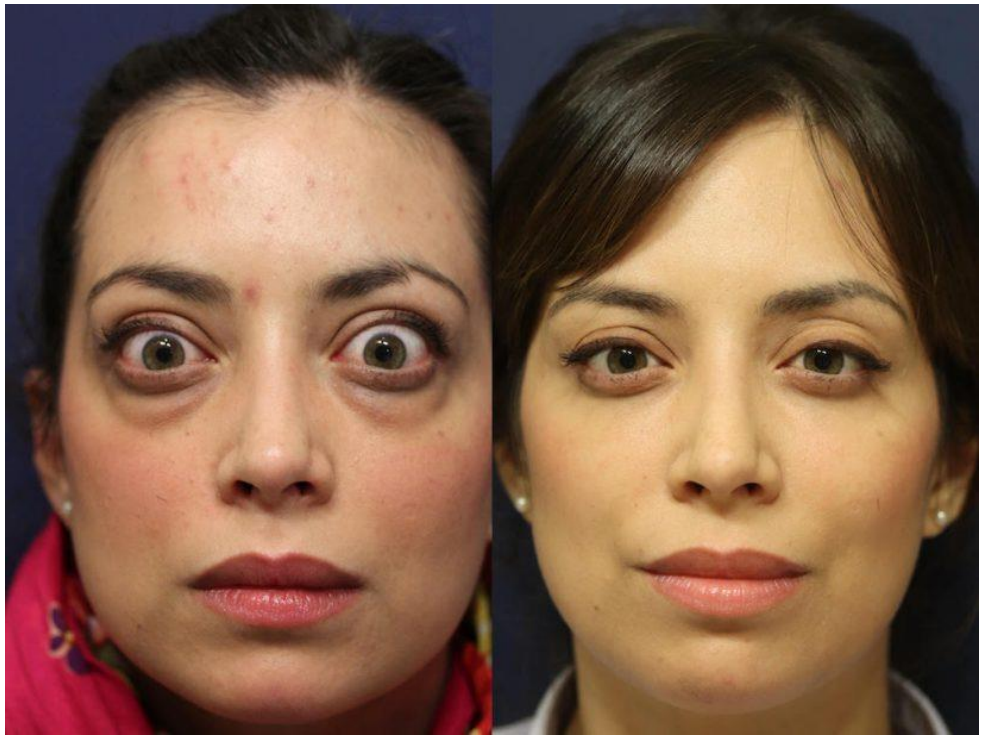
Graves' disease	Thyroid stimulating hormone
Hashimoto's thyroiditis	Thyroid peroxidase Thyroglobulin Pendrin
Myasthenia gravis	Nicotinic acetylcholine receptor Muscle-specific tyrosine kinase
Multiple sclerosis	Myelin oligodendrocyte glycoprotein
	Myelin basic protein



Miastenia gravis



Boala Graves

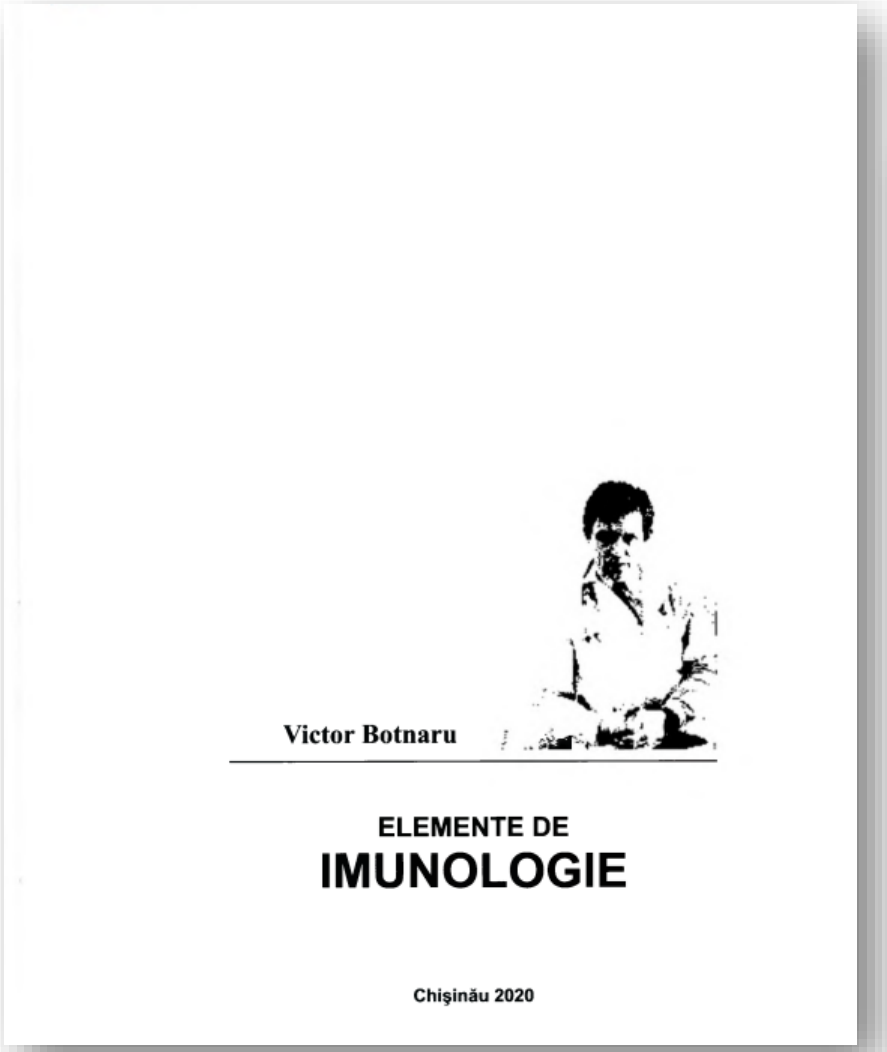


Teste imunodiagnostice pentru bolile autoimune

Tabelul 12.5

TESTE IMUNODIAGNOSTICE PENTRU BOLILE AUTOIMUNE

Ținta imunologică	Exemple de teste diagnostice
Disfuncții ale sistemului imun înnăscut	HLG, proteine de fază acută (CRP), viteza de sedimentare a eritrocitelor (VSH), activitatea complementului (CH50, C3, C4), ceruloplasmina, feritina, fibrinogenul, haptoglobina, albumina; procalcitonina
Disfuncții ale sistemului imun dobândit	Anticorpii anti-nucleari (valori și distribuție la nivel celular) (ANA) Autoanticorpi celulari specifici Factor reumatoid (IgM împotriva porțiunii Fc a IgG) Anticorpi anti-peptide ciclice citrulinate (anti-CCP) Anticorpi anti-fosfolipide Anticorpi anti-citoplasma polinuclearelor neutrofe (ANCA) Crioglobuline Autoanticorpi anti-coagulant/anti-cardiolipina/aPL
Studii moleculare și genetice	Imunofenotipare HLA Defecte monogenice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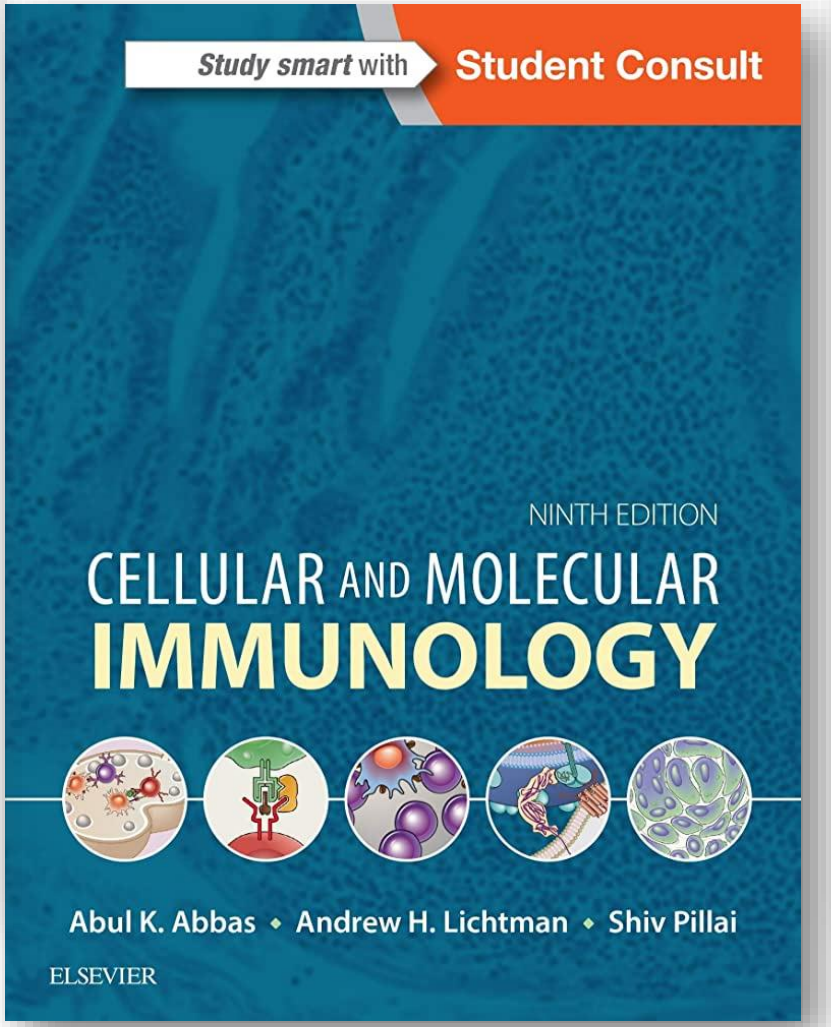
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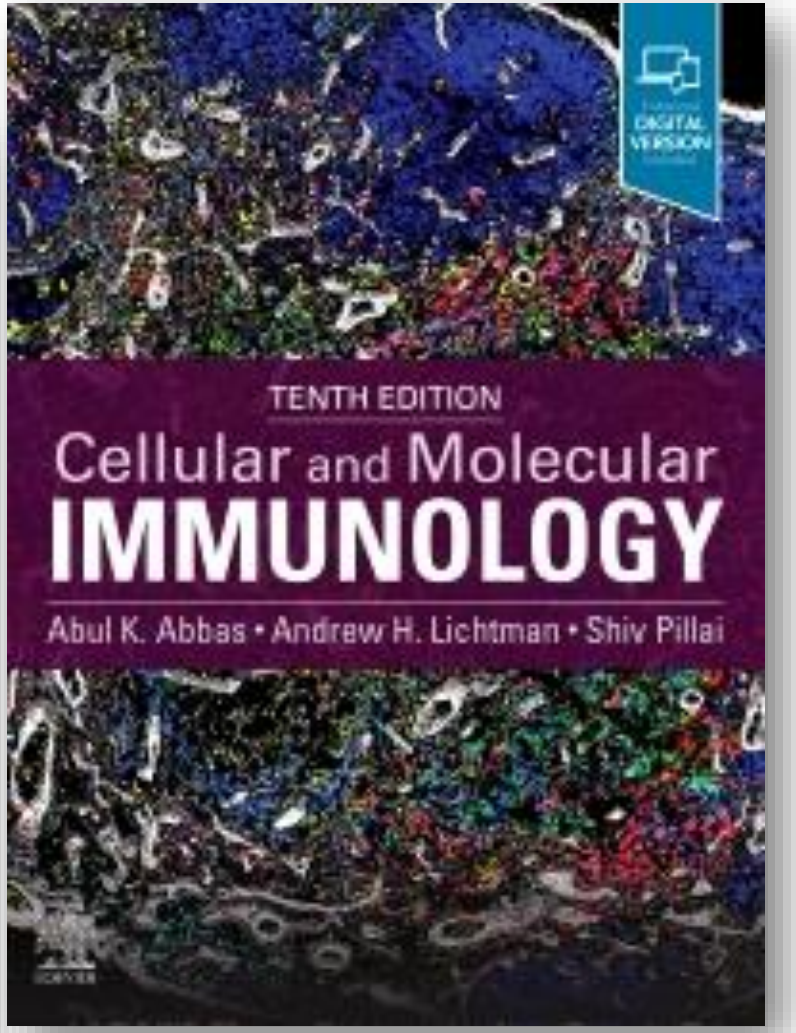
DIGITAL VERSION
TENTH EDITION
Cellular and Molecular
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