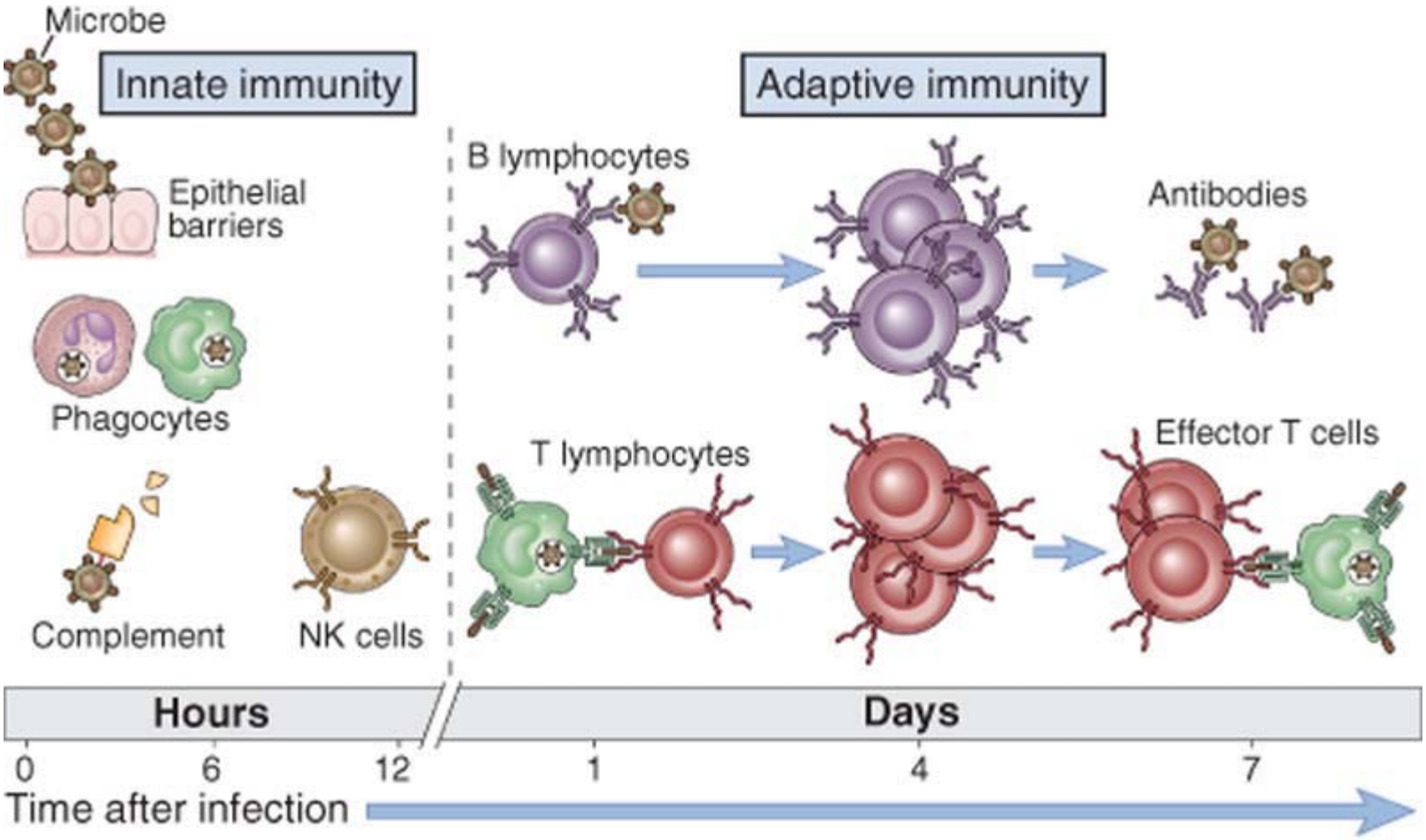
PROGRAM

30. 11/11: Ipersensitivity
32. 12/11: Seminar (antibody libraries)
34. 13/11: Ipersensitivity (Type 2/3)
36. 18/11: Ipersensitivity (Type 4)
38. 20/11: Ipersensitivity (Type 1)
40. 25/11: Vaccines
42. 27/11: Transplantation
44. 02/12: Immudeficencies
46. 04/12: Discussion (CAR-T cells)
48. 09/12: Seminar-Discussion (autoimmune diseases)

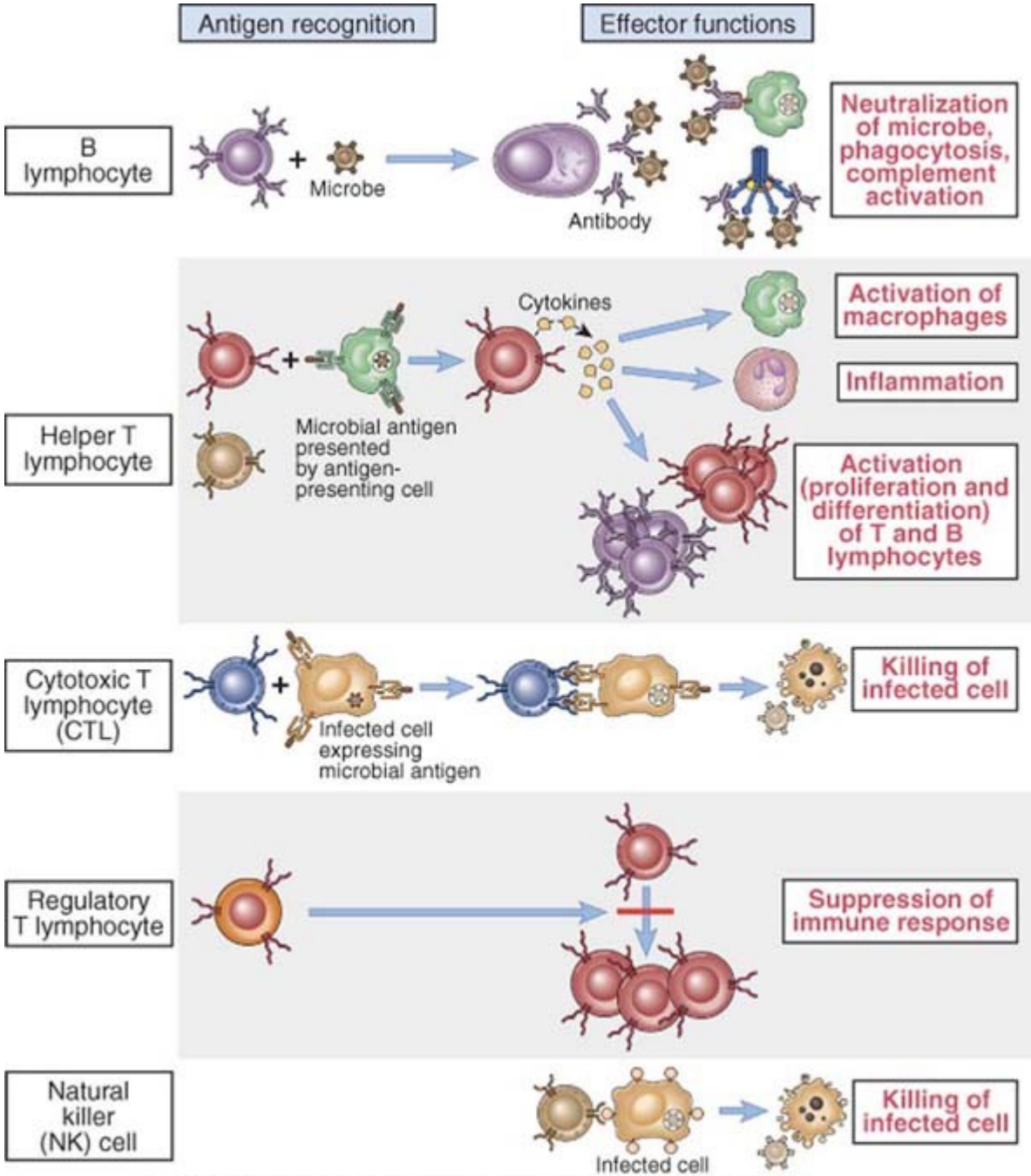
16/12: TEST

IPERsensitivity

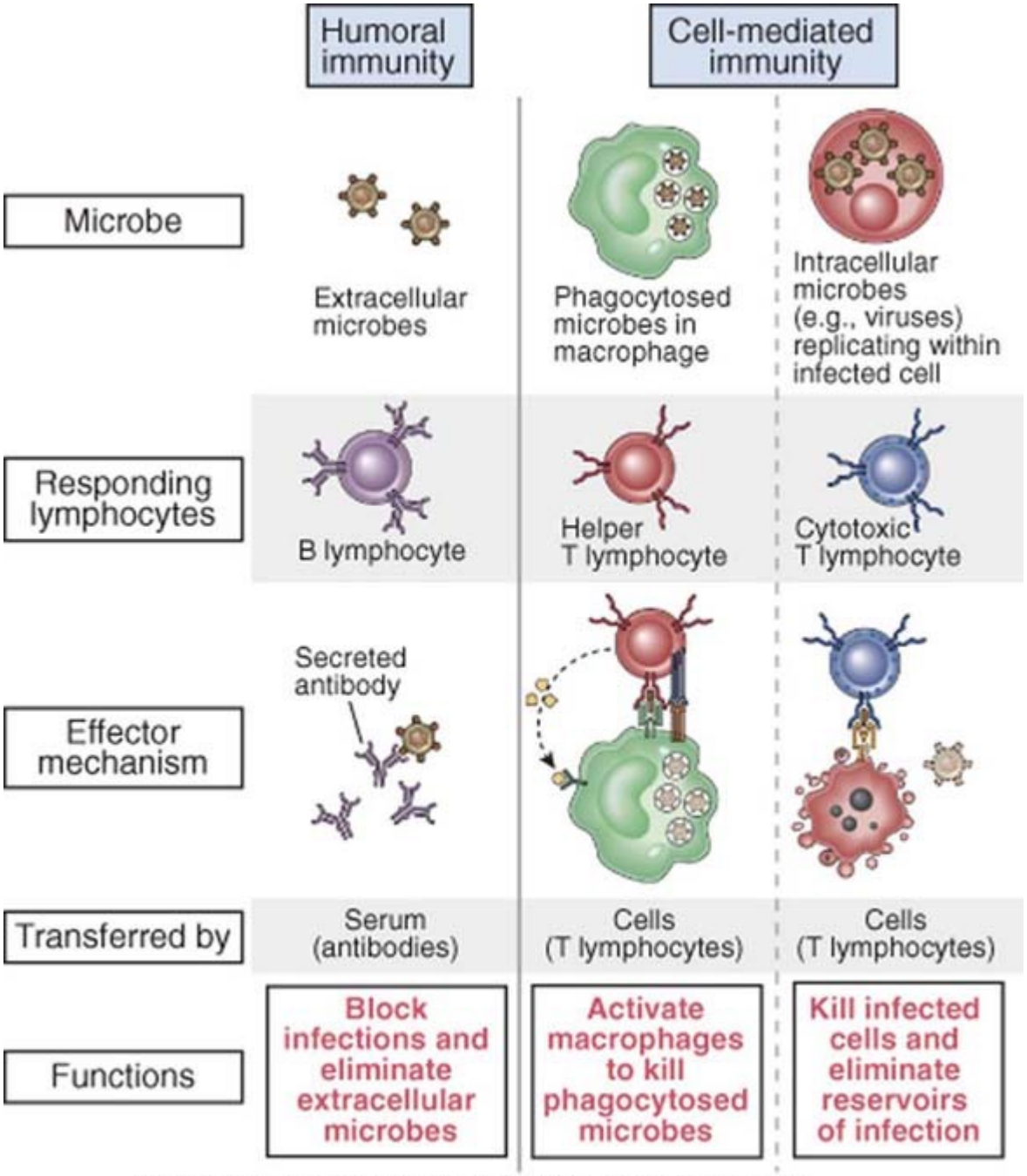
The immune system



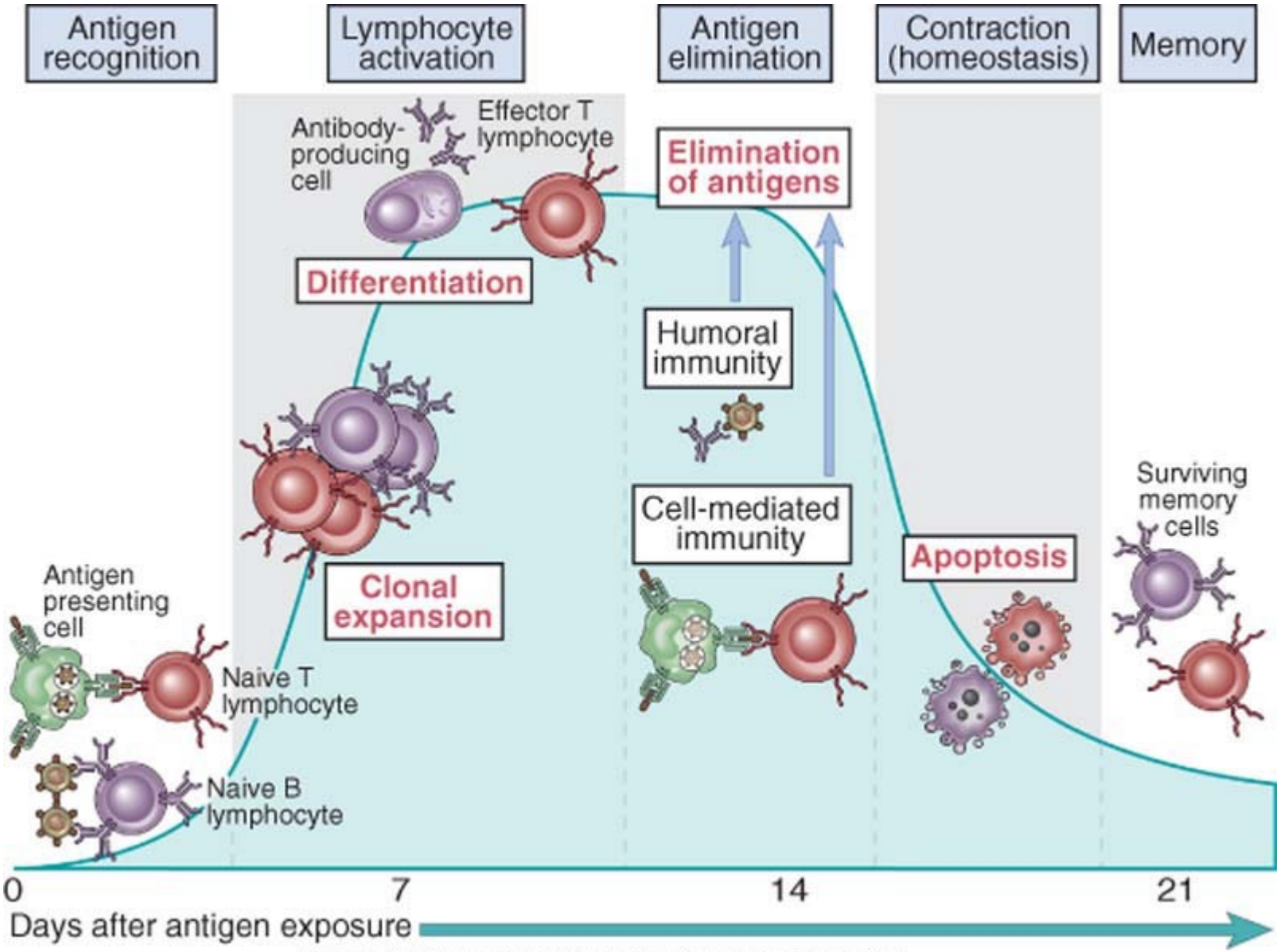
Lymphocytes



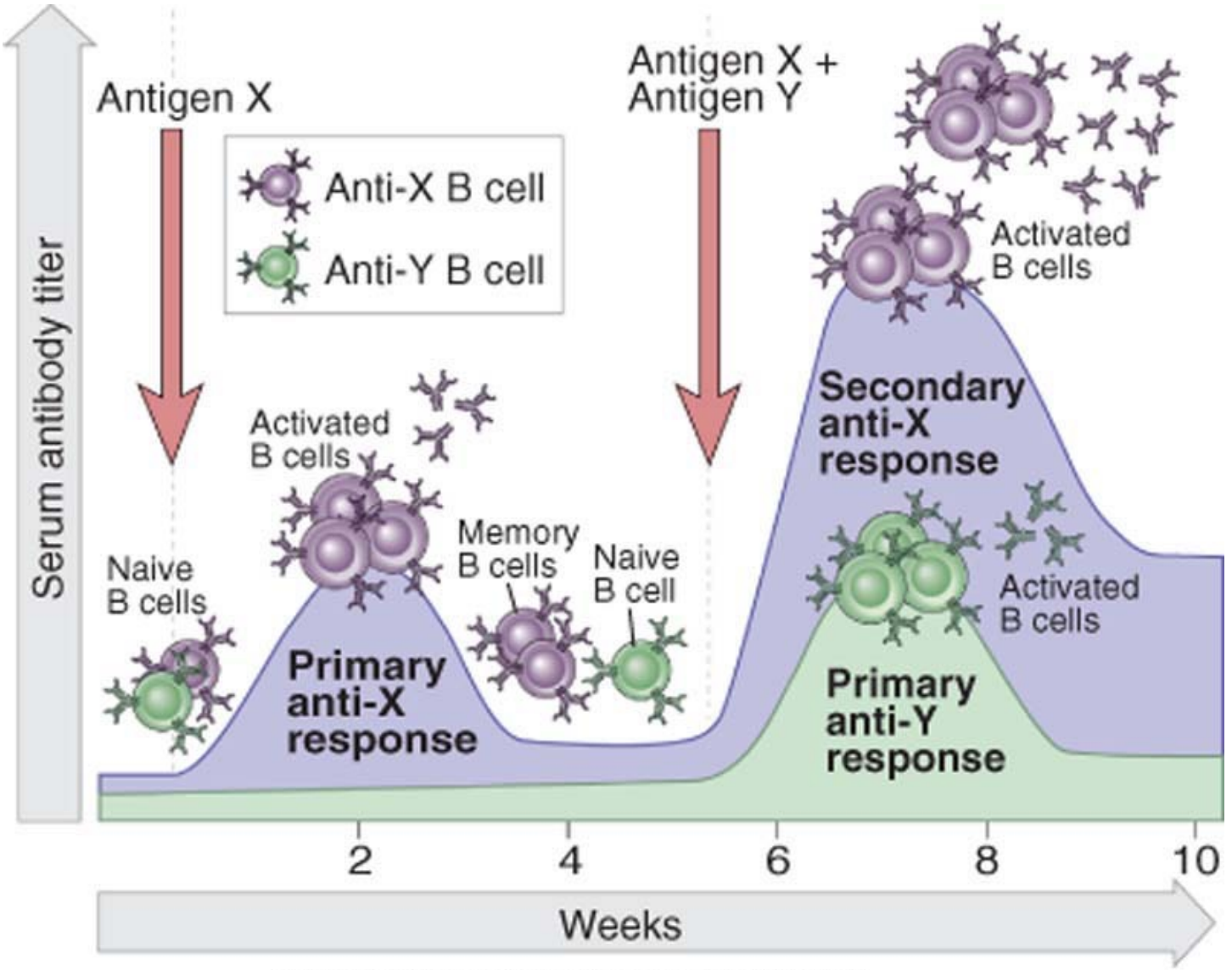
Immune response



Phases of adaptive immune response

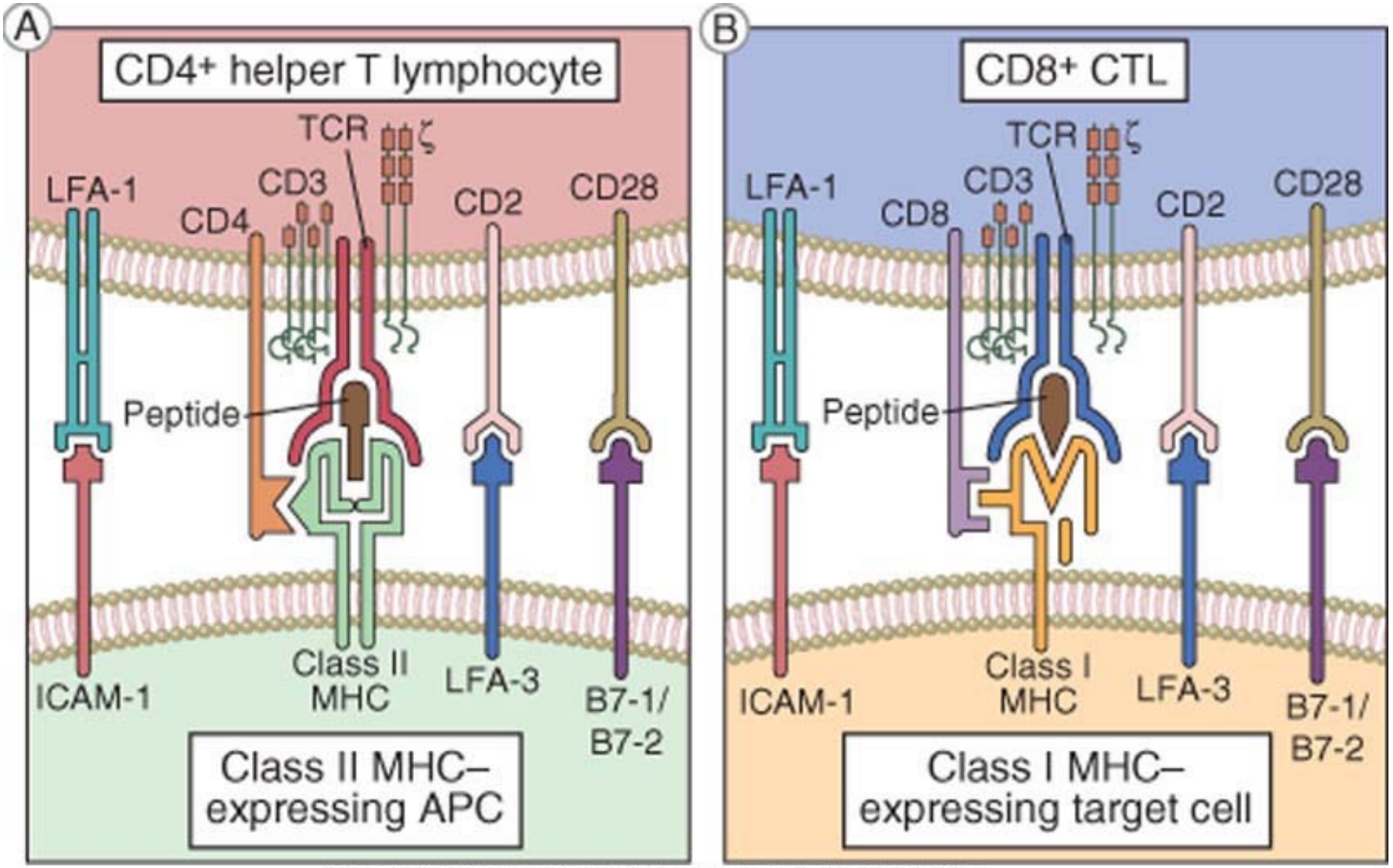


Specificity, resolution and memory



Control of Immune Response

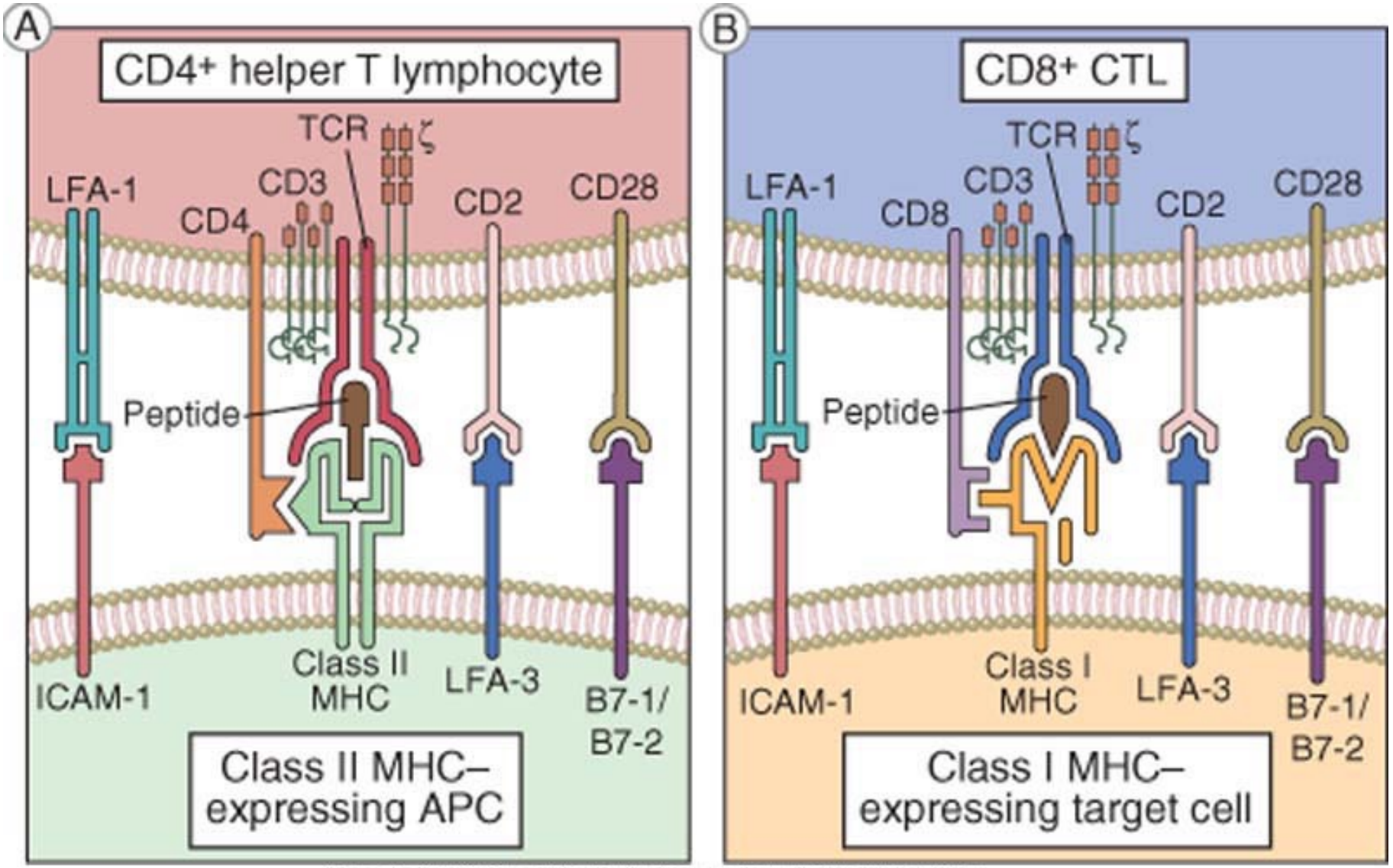
- **Antigen**



Abbas et al: Cellular and Molecular Immunology, Updated 6th Edition.

Control of Immune Response

- **Antigen**
- **Lymphocytes half-life**
- **Treg Lymphocytes**
- **Complexity of the system (request of several costimulatory molecules)**



Abbas et al: Cellular and Molecular Immunology, Updated 6th Edition.

Hypersensitivity disorders: disorders caused by immune responses

….. Normally, immune responses eradicate infectious pathogens without serious injury to host tissues. However, these responses are sometimes inadequately controlled, inappropriately targeted to host tissues, or triggered by commensal microorganisms or environmental antigens that are usually harmless. In these situations, the normally beneficial immune response is the cause of disease.

TABLE 19.1 Classification of Hypersensitivity Diseases

Type of Hypersensitivity	Pathologic Immune Mechanisms	Mechanisms of Tissue Injury and Disease
Immediate: Type I	IgE antibody, Th2 cells	Mast cells, eosinophils, and their mediators (vasoactive amines, lipid mediators, cytokines)
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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 (Th1 and Th17 cells) 2. $CD8^+$ CTLs	1. Cytokine-mediated inflammation and macrophage activation 2. Direct target cell killing, cytokine-mediated inflammation

CTLs, Cytotoxic T lymphocytes; *Ig,* immunoglobulin.

The hypersensitivity reactions

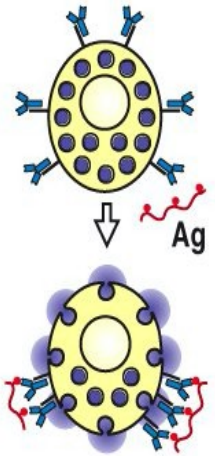
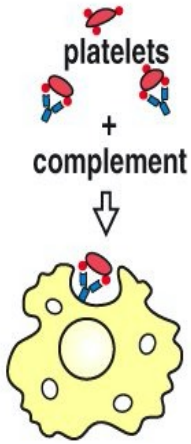
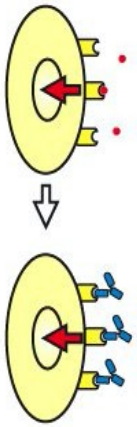
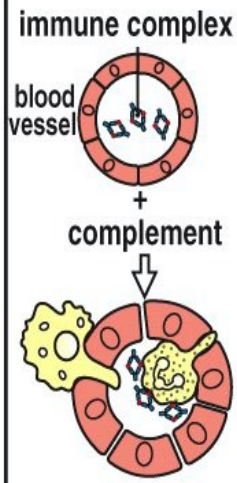
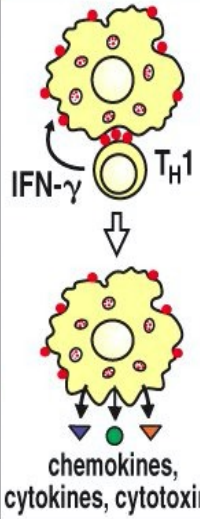
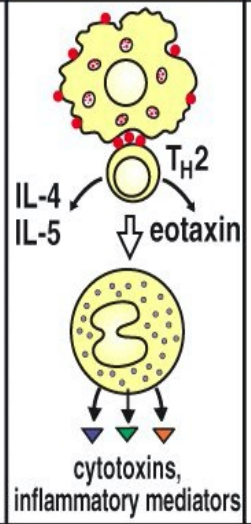
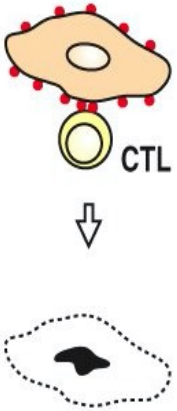
	Type I	Type II		Type III	Type IV		
Immune reactant	IgE	IgG		IgG	T_H1 cells	T_H2 cells	CTL
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Antibody alters signaling	Complement, Phagocytes	Macrophage activation	IgE production, Eosinophil activation, Mastocytosis	Cytotoxicity
							
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (eg, penicillin)	Chronic urticaria (antibody against FCεR1α)	Serum sickness, Arthus reaction	Contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Contact dermatitis

Figure 12-2 Immunobiology, 6/e. (© Garland Science 2005)

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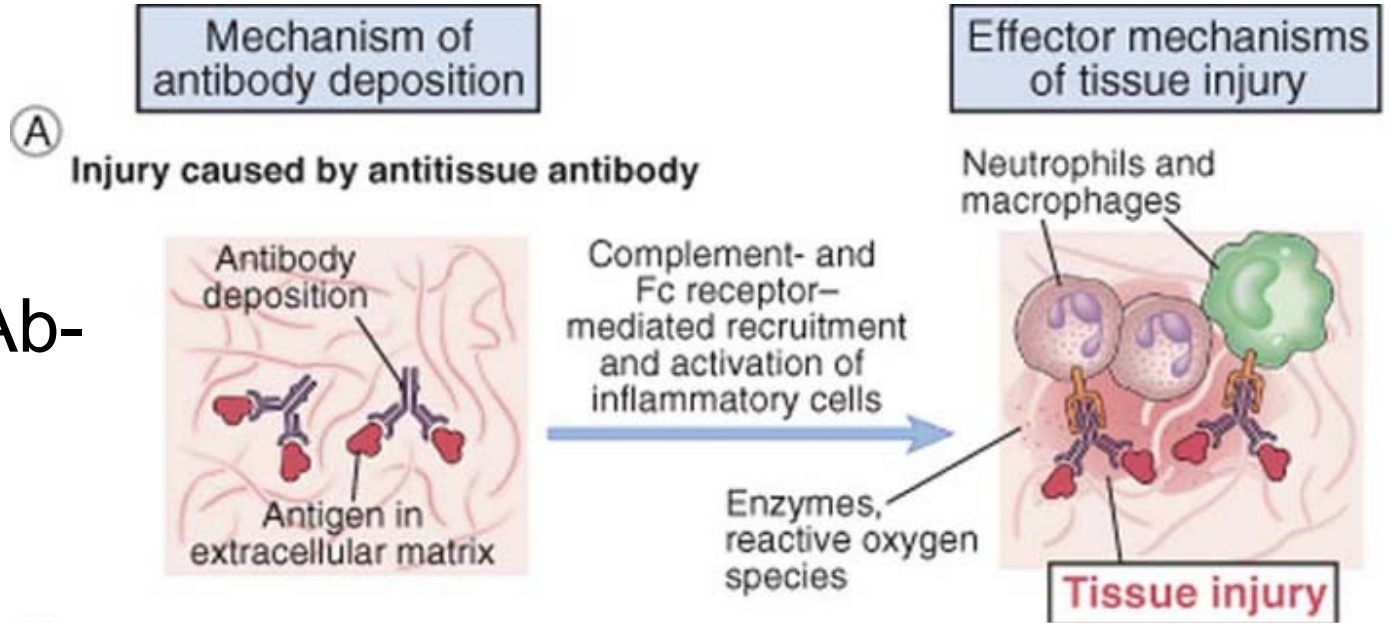
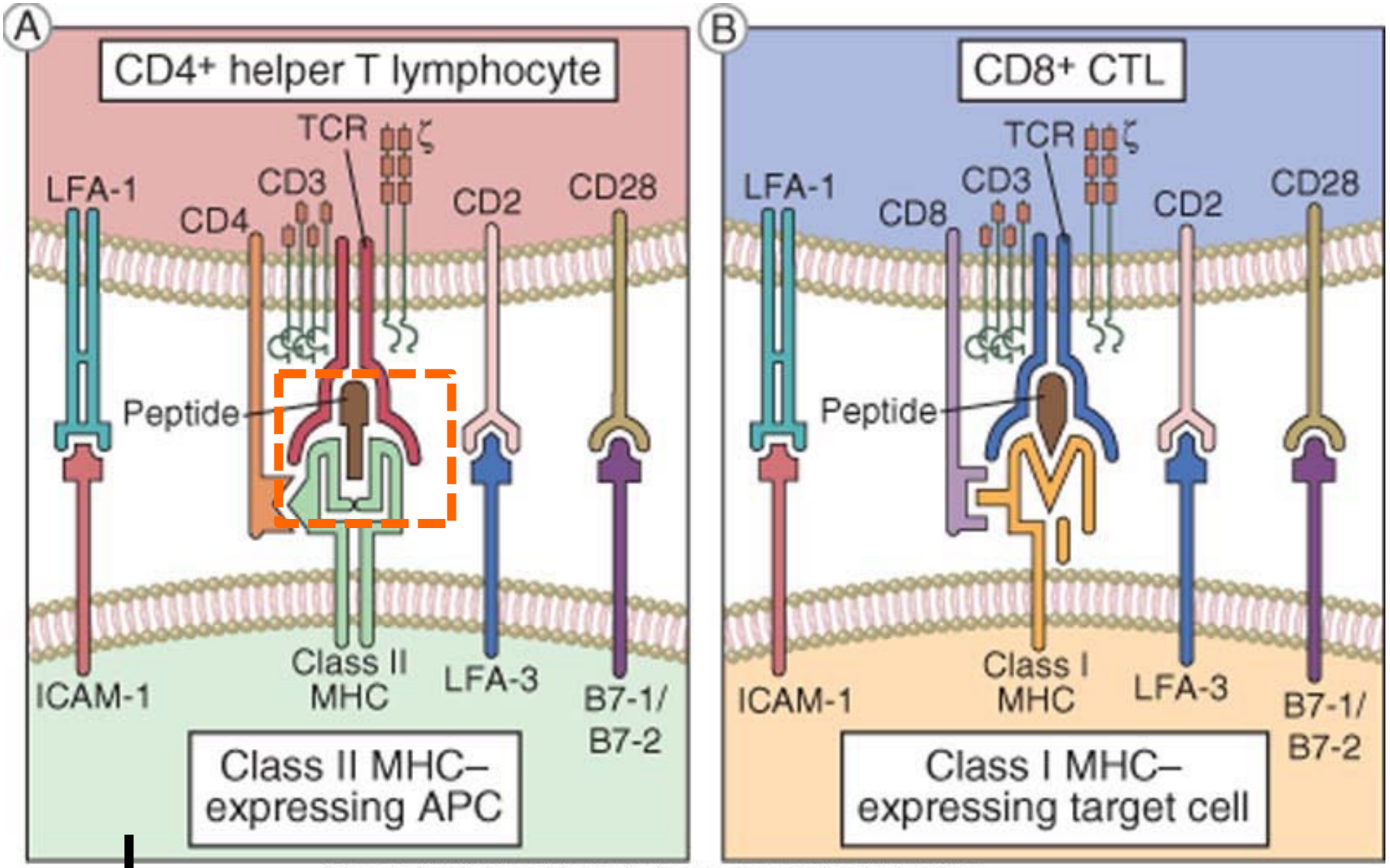
CTLs, Cytotoxic T lymphocytes; *Ig,* immunoglobulin.

Examples of Ab-mediated disorders





TH2 Response

Effector mechanisms of Ab-mediated disorders?

Effector mechanisms of Ab-mediated disorders

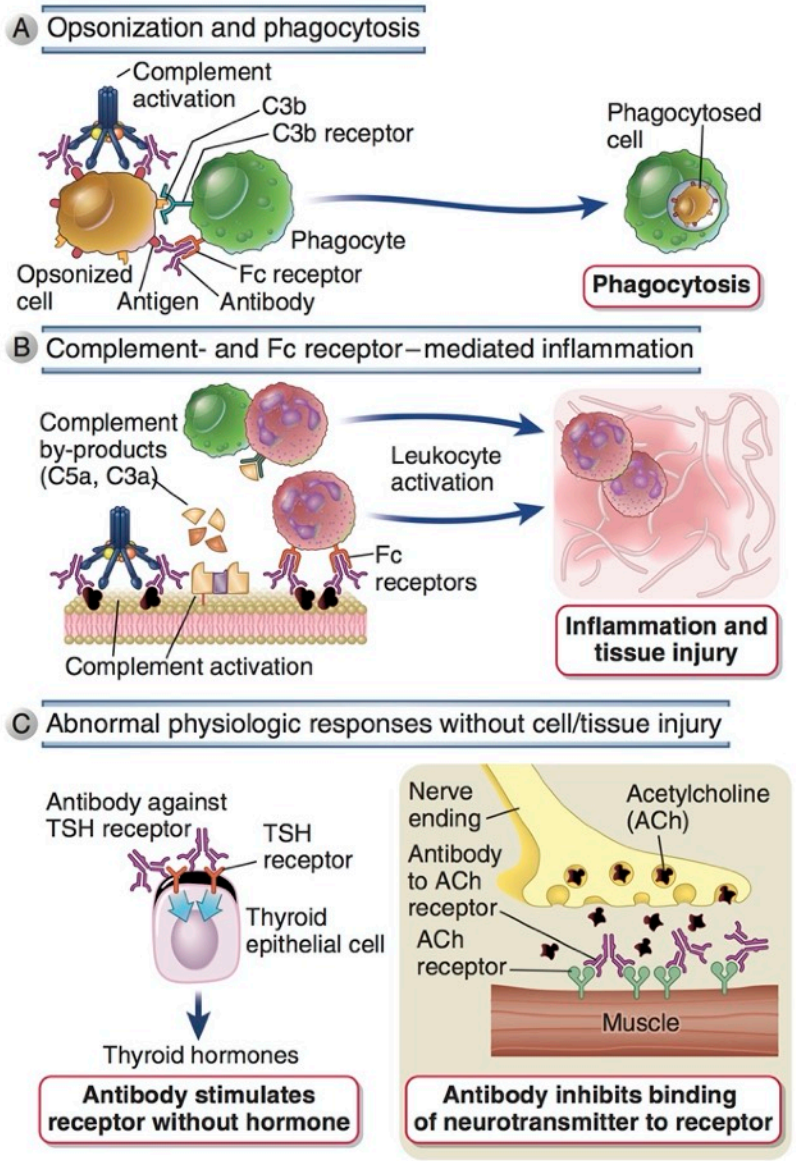


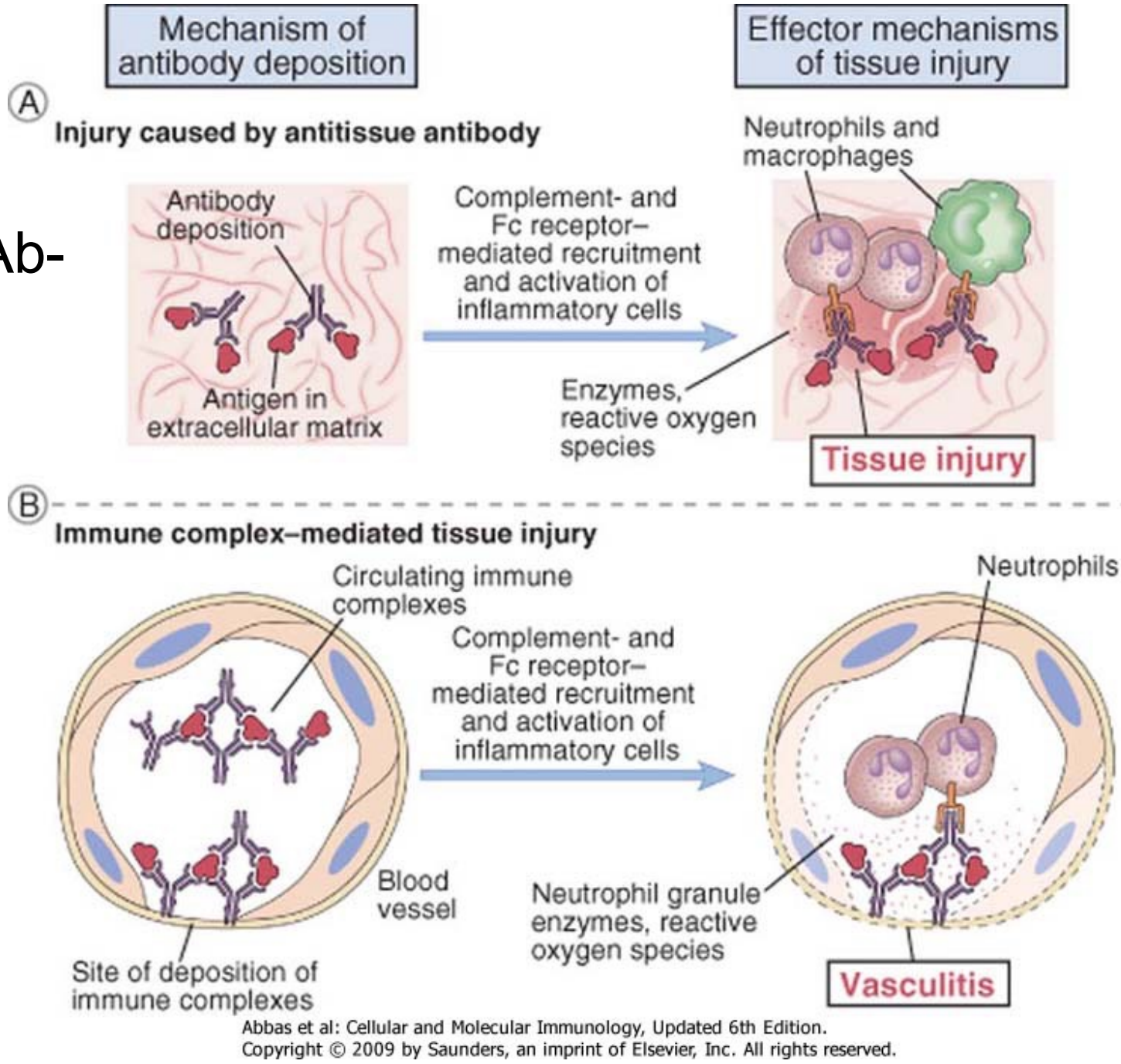
FIGURE 19.2 Effector mechanisms of antibody-mediated disease. A, Antibodies opsonize cells and may activate complement, generating complement products that also opsonize cells, leading to phagocytosis of the cells through phagocyte Fc receptors or C3b receptors. **B,** Antibodies recruit leukocytes by binding to Fc receptors or by activating complement and thereby releasing by-products that are chemotactic for leukocytes. **C,** Antibodies specific for cell surface hormone receptors or neurotransmitter receptors interfere with normal physiology. For example, in Graves' disease *(left panel)* autoantibodies specific for thyroid stimulating hormone (TSH) receptors in the thyroid gland stimulate the activity of the receptors even in the absence of TSH, causing excess thyroid hormone release (hyperthyroidism). In myasthenia gravis *(right panel)*, autoantibodies specific for the acetylcholine receptor on muscle cells block the action of acetylcholine, leading to paralysis.

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

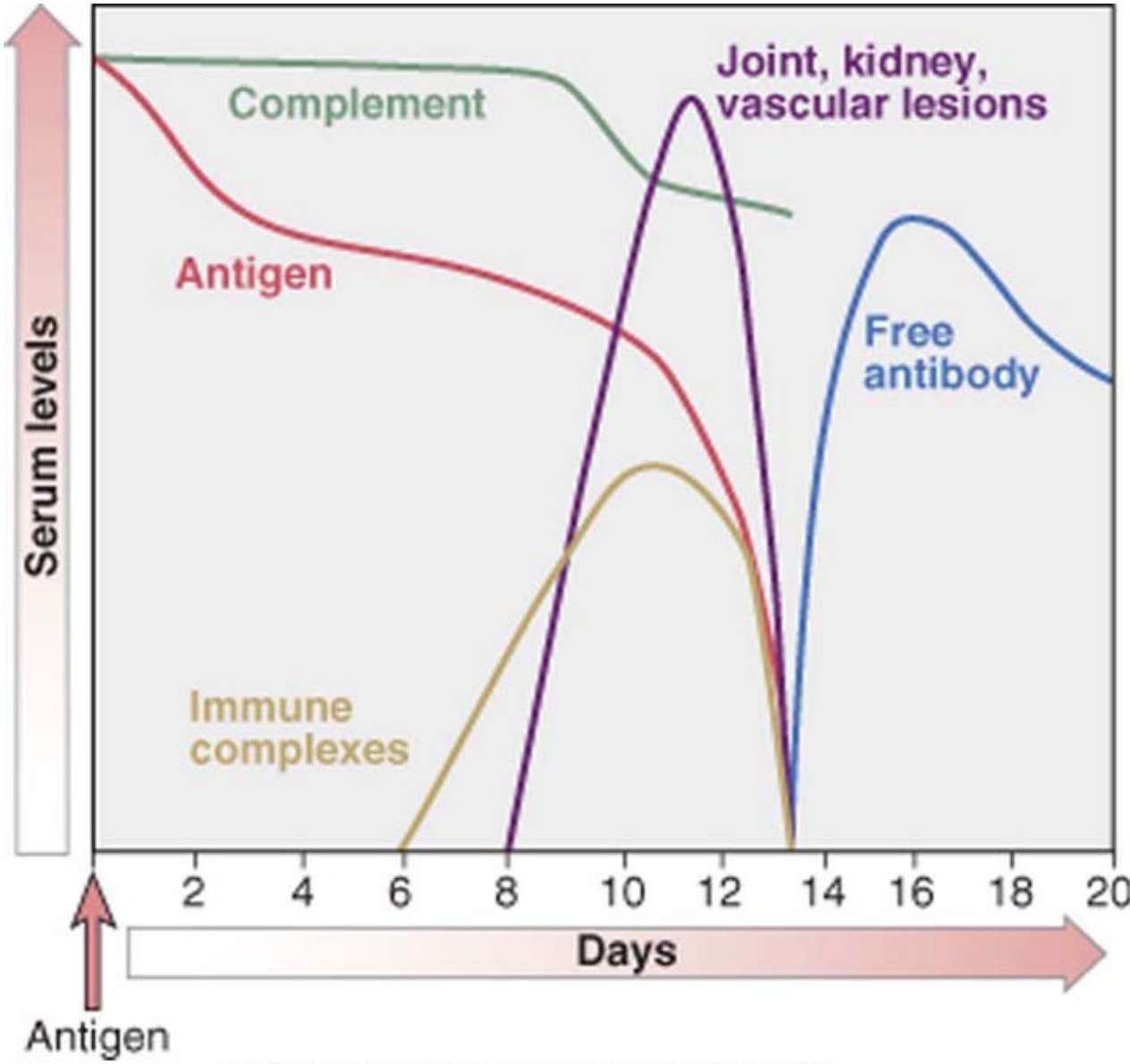
Disease	Target Antigen	Mechanisms of Disease	Clinicopathologic Manifestations
Autoimmune hemolytic anemia	Erythrocyte membrane proteins	Opsonization and phagocytosis of erythrocytes, complement-mediated lysis	Hemolysis, anemia
Autoimmune thrombocytopenic purpura	Platelet membrane proteins (gpIIb-IIIa 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

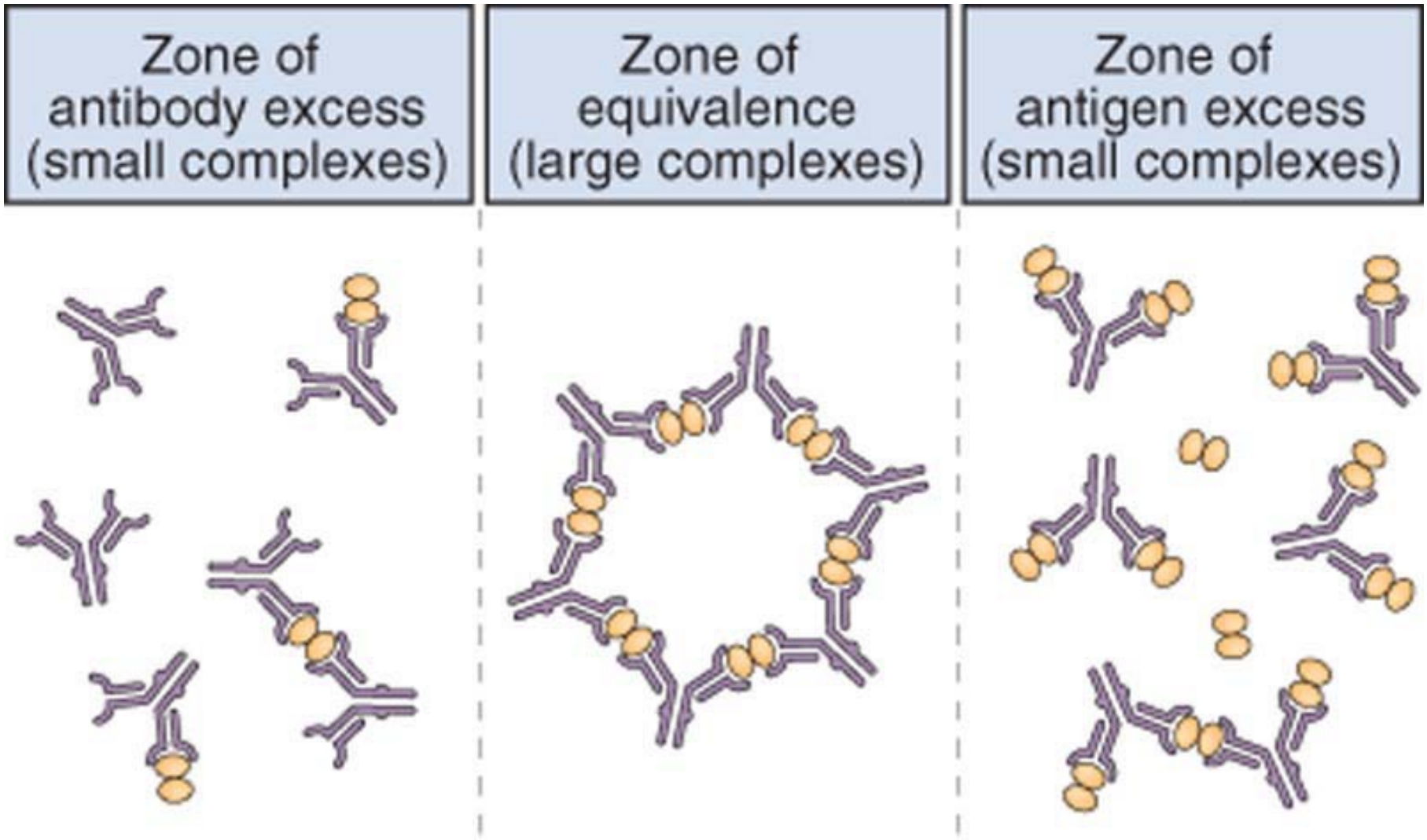
ANCA, Anti-neutrophil cytoplasmic antibodies; *TSH*, thyroid-stimulating hormone.

Examples of Ab-mediated disorders



Sequence of the immunological response

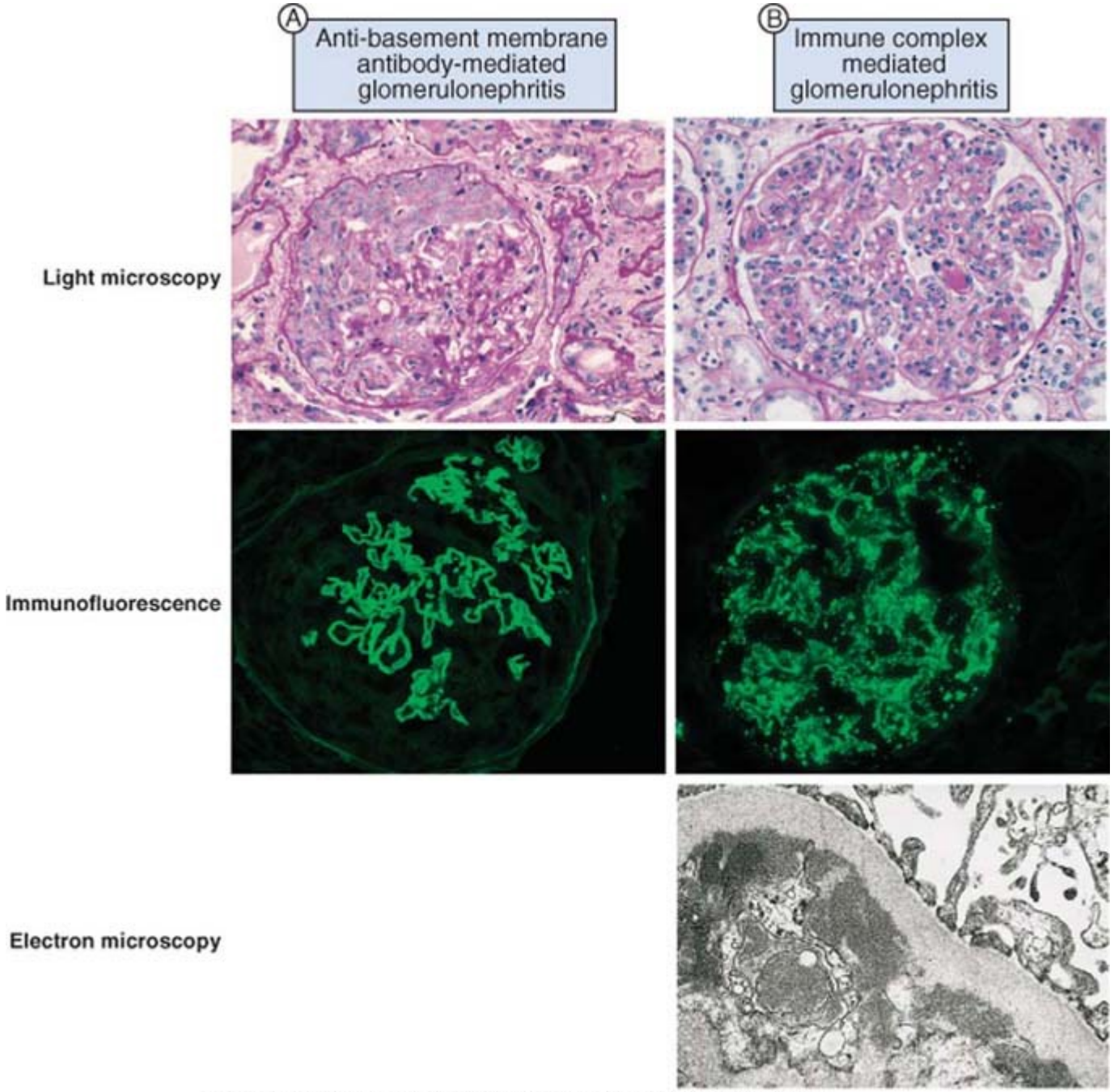




FcR	Affinity for immunoglobulin	Cell Distribution	Function
Fc γ RI (CD64)	High (Kd ~ 10^{-9} M) binds IgG1 and IgG3	Macrophages, neutrophils; also eosinophils	Phagocytosis, activation of phagocytes
Fc γ RIIA (CD32)	Low (Kd > 10^{-7} M)	Macrophages, neutrophils; eosinophils, platelets	Phagocytosis; cell activation (inefficient)
Fc γ RIIB (CD32)	Low (Kd > 10^{-7} M)	B lymphocytes, dendritic cells, macrophages	Feedback inhibition of B cells, macrophages, dendritic cells
Fc γ RIIIA (CD16)	Low (Kd > 10^{-6} M)	NK cells	Antibody-dependent cell-mediated cytotoxicity
Fc γ RIIIB (CD16)	Low (Kd > 10^{-6} M) GPI-linked protein	Neutrophils, other cells	Phagocytosis (inefficient)
Fc ε RI	High (Kd > 10^{-10} M) binds monomeric IgE	Mast cells, basophils, eosinophils	Cell activation (degranulation)
Fc ε RII (CD23)	Low (Kd > 10^{-7} M)	B lymphocytes, eosinophils, Langerhans cells	Unknown
Fc α R (CD89)	Low (Kd > 10^{-6}M)	Neutrophils, eosinophils, monocytes	Cell activation?

TABLE 19.3 Examples of Human Immune Complex–Mediated Diseases

Disease	Antigen Involved	Clinicopathologic Manifestations
Systemic lupus erythematosus	DNA, nucleoproteins, others	Nephritis, arthritis, vasculitis
Polyarteritis nodosa	Hepatitis B virus surface antigen (in some cases)	Vasculitis
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigens	Nephritis
Serum sickness	Various proteins	Arthritis, vasculitis, nephritis



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CTLs, Cytotoxic T lymphocytes; *Ig,* immunoglobulin.

Cell-Mediated Immunity

- The effector cells involved in these processes are cytotoxic T-lymphocytes (CTLs), NK-cells and Th cells

Phagocytosis and killing of intracellular pathogens

Direct cell killing by cytotoxic T cells

Direct cell killing by NK cells

These responses are especially important for destroying intracellular bacteria, eliminating viral infections and destroying tumor cells

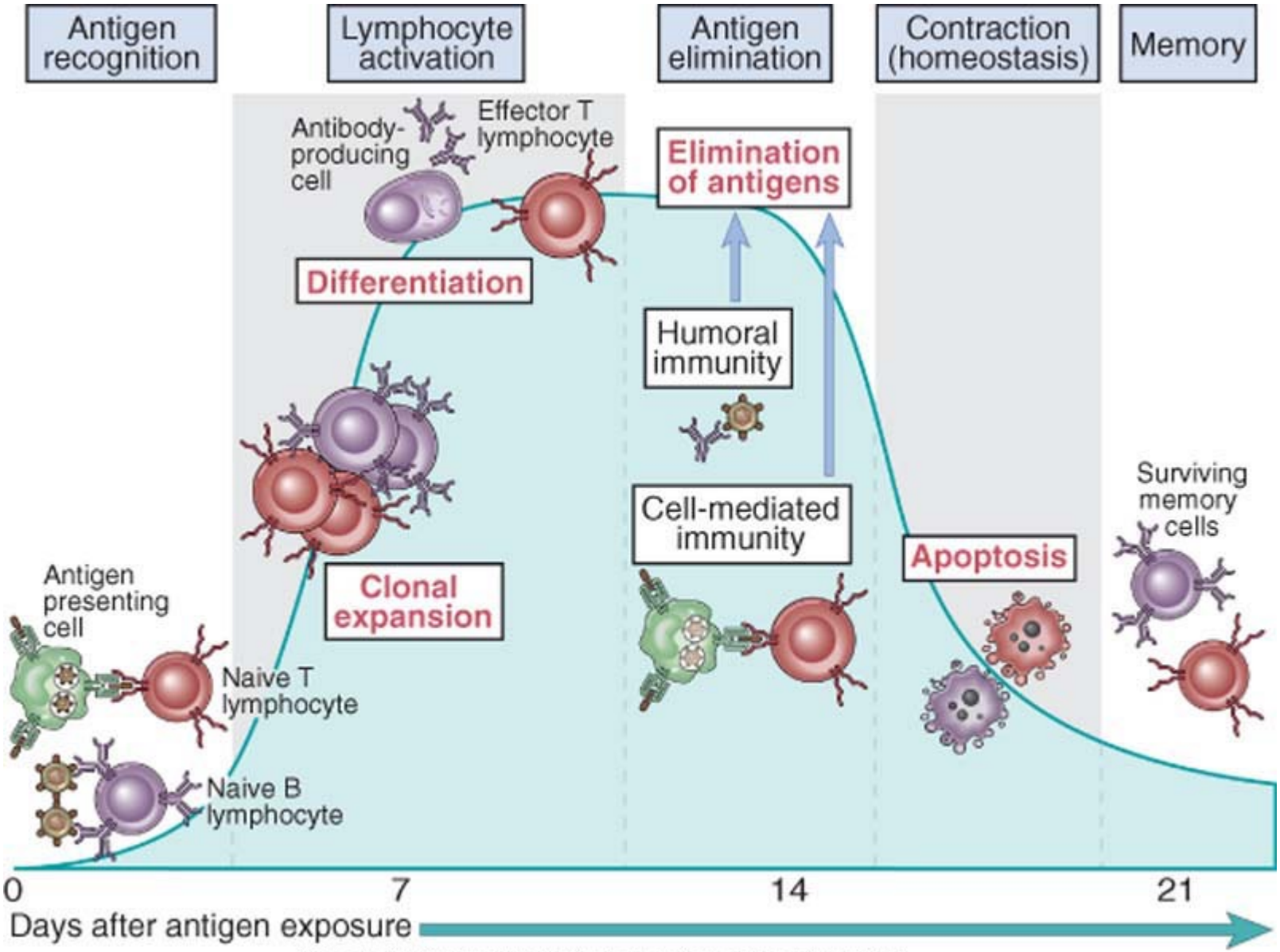
- Response to microbes residing within the phagosomes is mediated by effector CD4 Th1 cells
- Microbes that infect and replicate in non-phagocytic cells is mediated by CD8
- T cell-dependent macrophage activation and inflammation may damage normal tissues

Killing by cytotoxic T cells

- release some substances known as perforin ,Granzyme A,B ,C and serglycin and granulysin
- the CTL may release lymphokines and/ or cytokines

Type IV hypersensitivity

- DTH (Delayed type hyper sensitivity)
- Is a T cell mediated inflammatory response, in which stimulation of T cells leads to macrophage activation and localized inflammation and edema within tissues.
- This effector T cell response is essential for the control of intracellular and other pathogens.
- If the response is excessive or against self Ags it can damage host tissues



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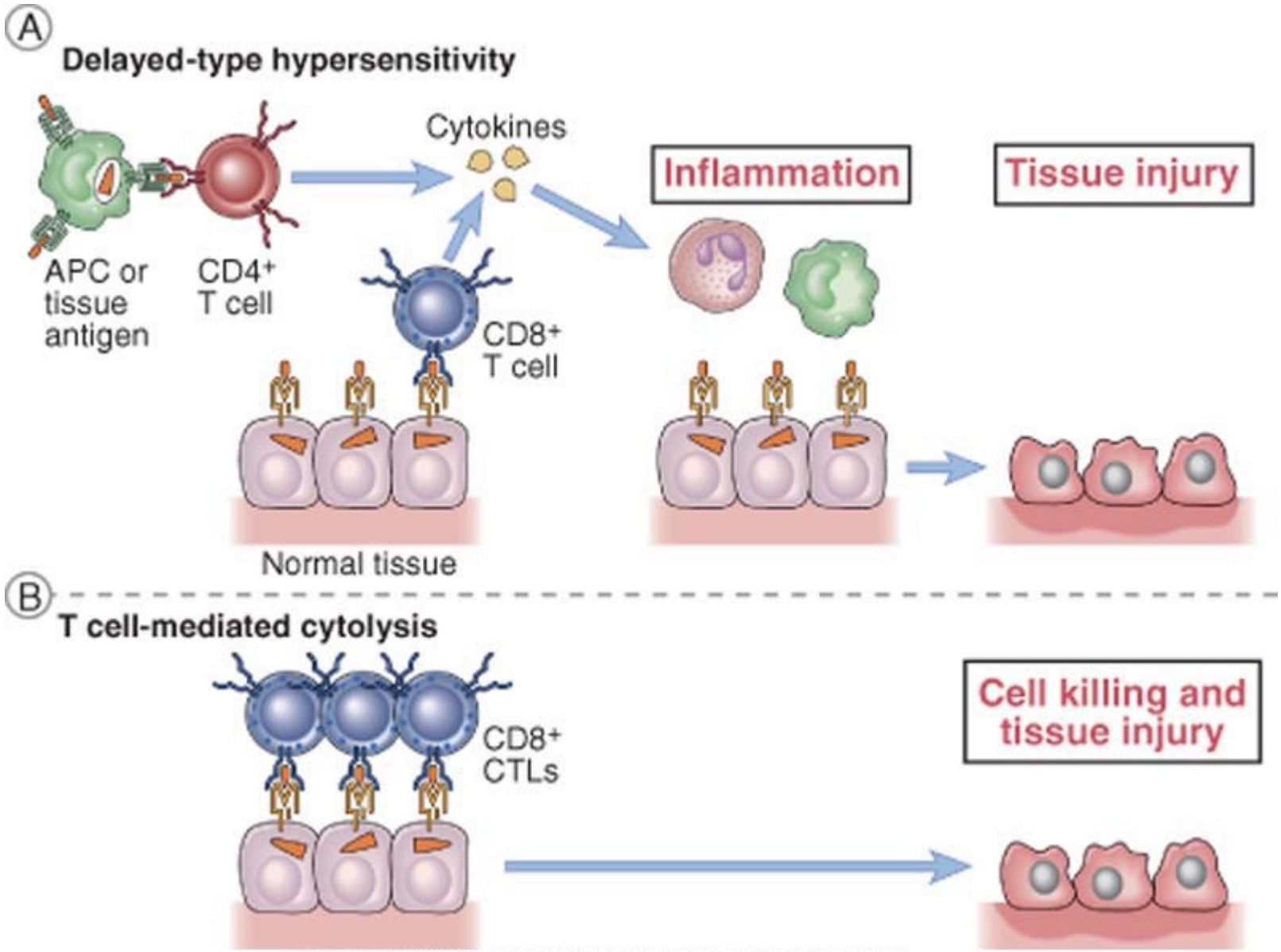
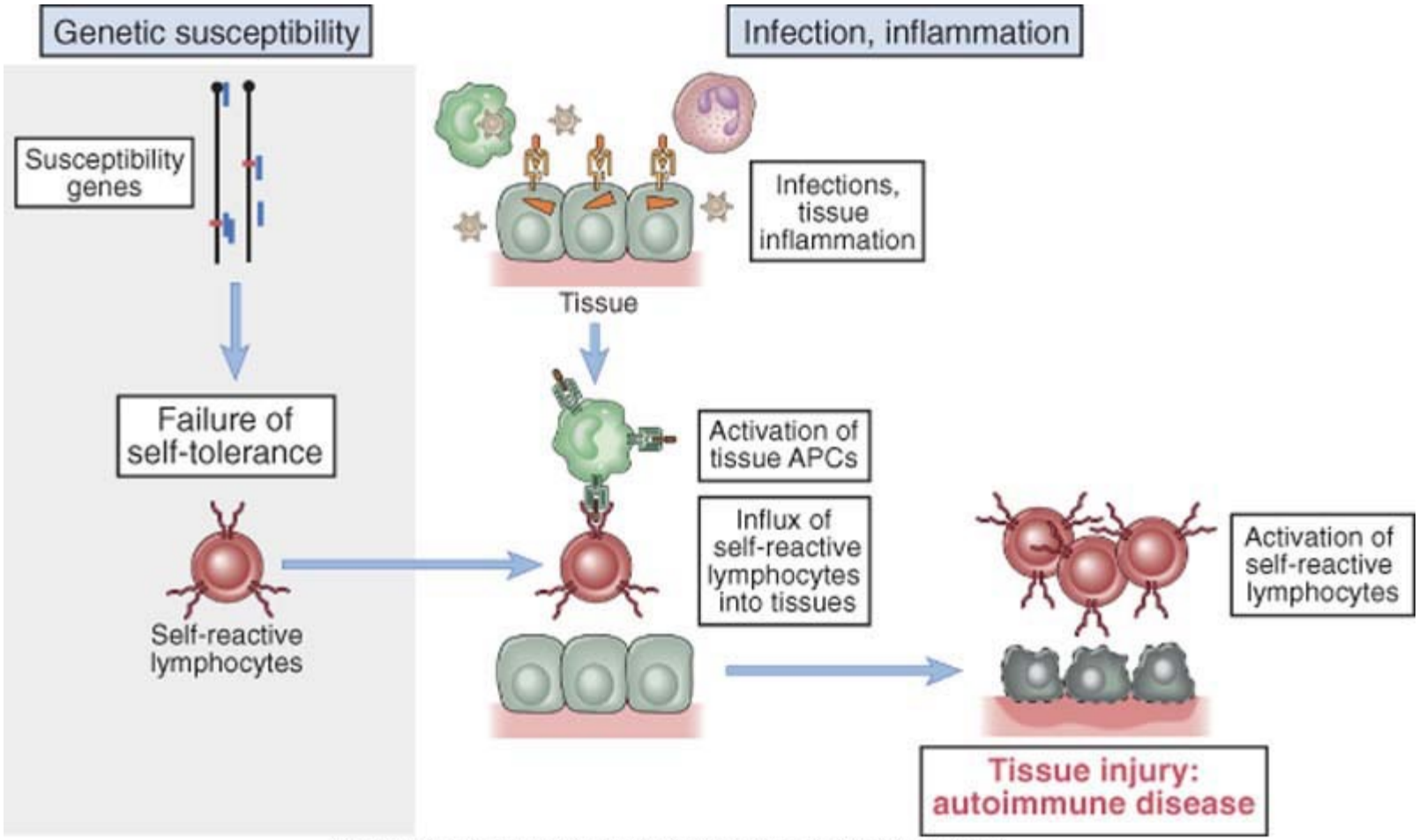
- This effector T cell response is essential for the control of intracellular and other pathogens.
- If the response is excessive or against self Ags it can damage host tissues
- Subsequent exposure of the sensitized individual to the exogenous Ag results in the recruitment of specific T cells to the site and development of a local inflammatory response over 24-72 hrs.

Mechanisms of T lymphocytes mediated disorders





Ipersensibilità di tipo ritardata

Dermatite da contatto

Può essere causata da alcuni metalli rari (zirconio) o sostanze vegetali (linfa di mango)

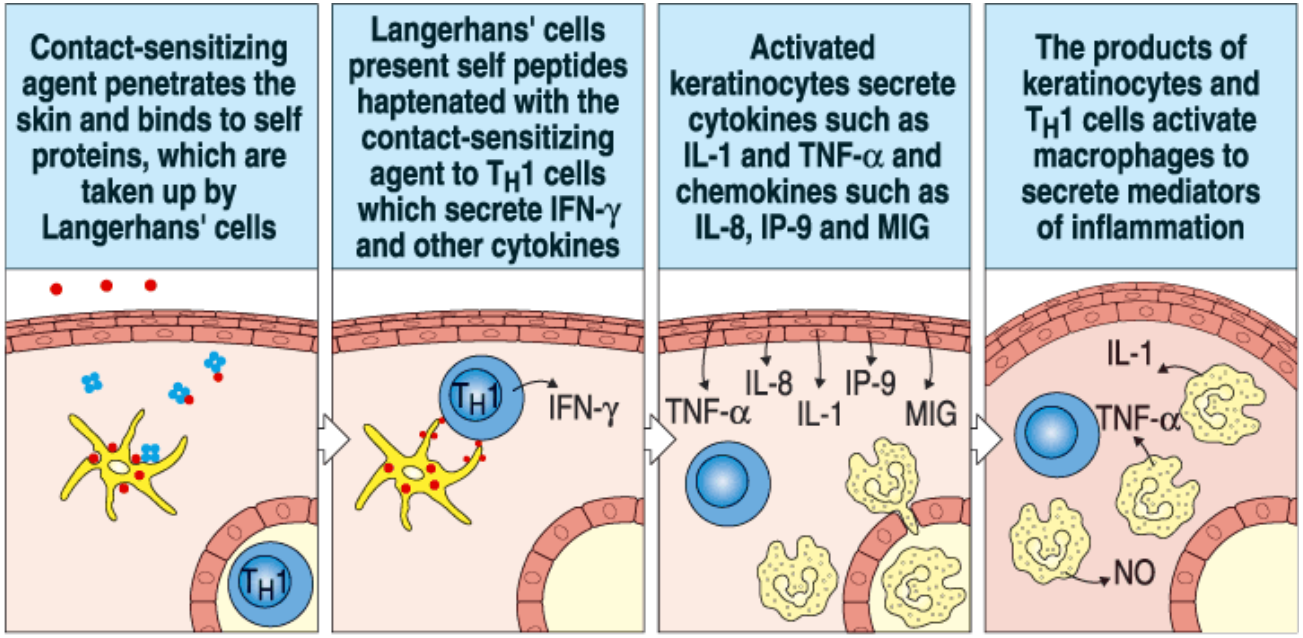


Fig 12.24 © 2001 Garland Science

*Un agente sensibilizzante è normalmente una piccola molecola (aptene) che penetra attraverso la pelle, lega proteine self, trasformandole in antigeni.