Corso di Laurea Magistrale in Biotecnologie Mediche
Università degli Studi di Napoli Federico II
Corso Integrato di Basi molecolari di patologie immunitarie e neurologiche

Immunopathology

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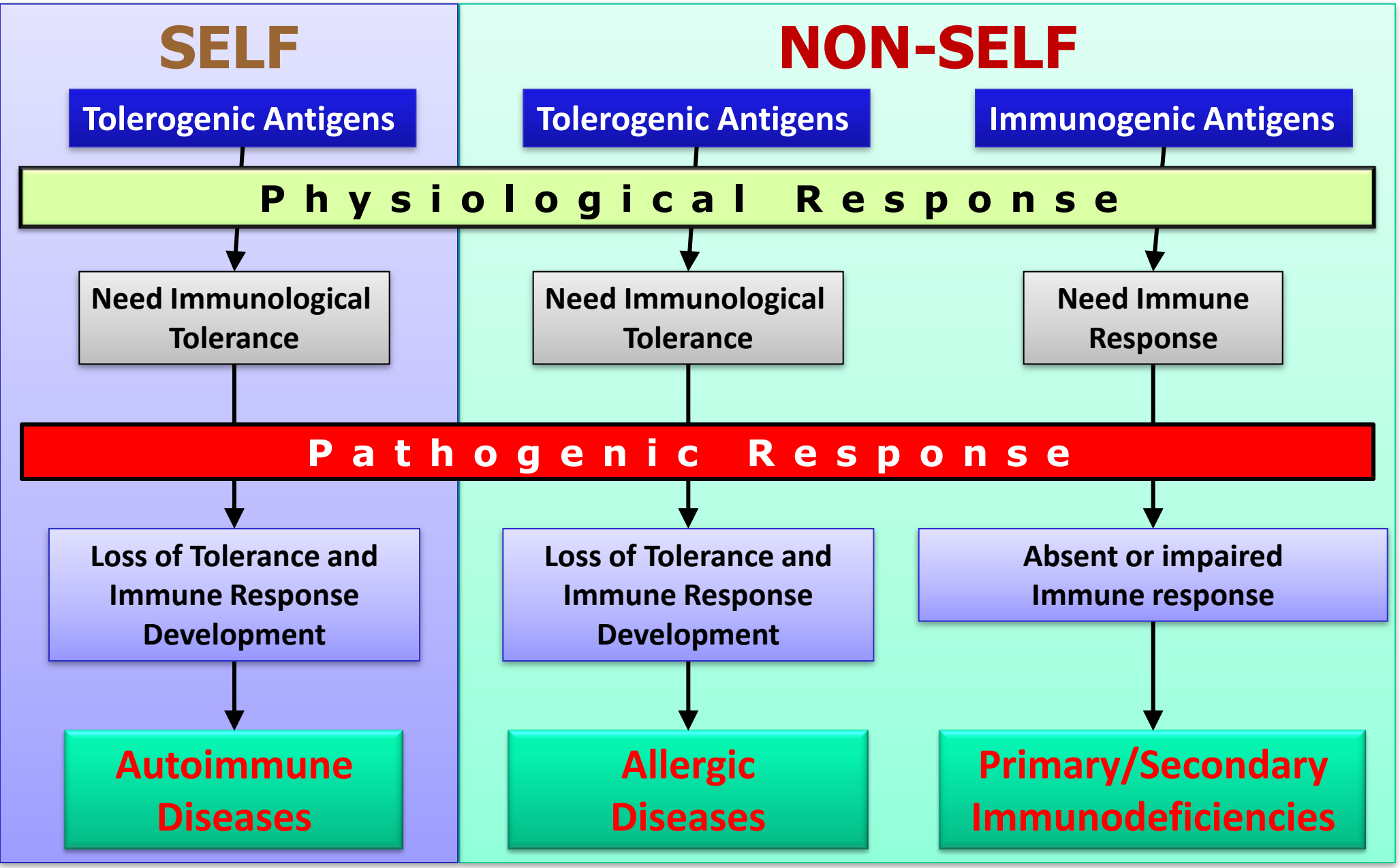
Action Field of Clinical Immunology



Classification of Hypersensitivity Reactions according to Gell and Coombs

- **Type I reactions (immediate or anaphylactic reactions)**
- **Type II reactions (cytotoxic reactions)**
- **Type III reactions (immune complex reactions)**
- **Type IV reactions (cell-mediated or delayed hypersensitivity reactions)**

Type I, II, and III reactions are immediate

Type IV reactions are delayed

Classification of Hypersensitivity Reactions according to Gell and Coombs

- **Type I reactions are immediate due to the presence of immunoglobulin E (IgE) produced after exposure to environmental factors called allergens (e.g. allergic diseases)**

- **Type II or cytotoxic reactions are due to the presence of antibodies (IgG o IgM) directed against cells or tissue antigens and can damage these elements or alterate their functions (e.g. transfusion reactions)**

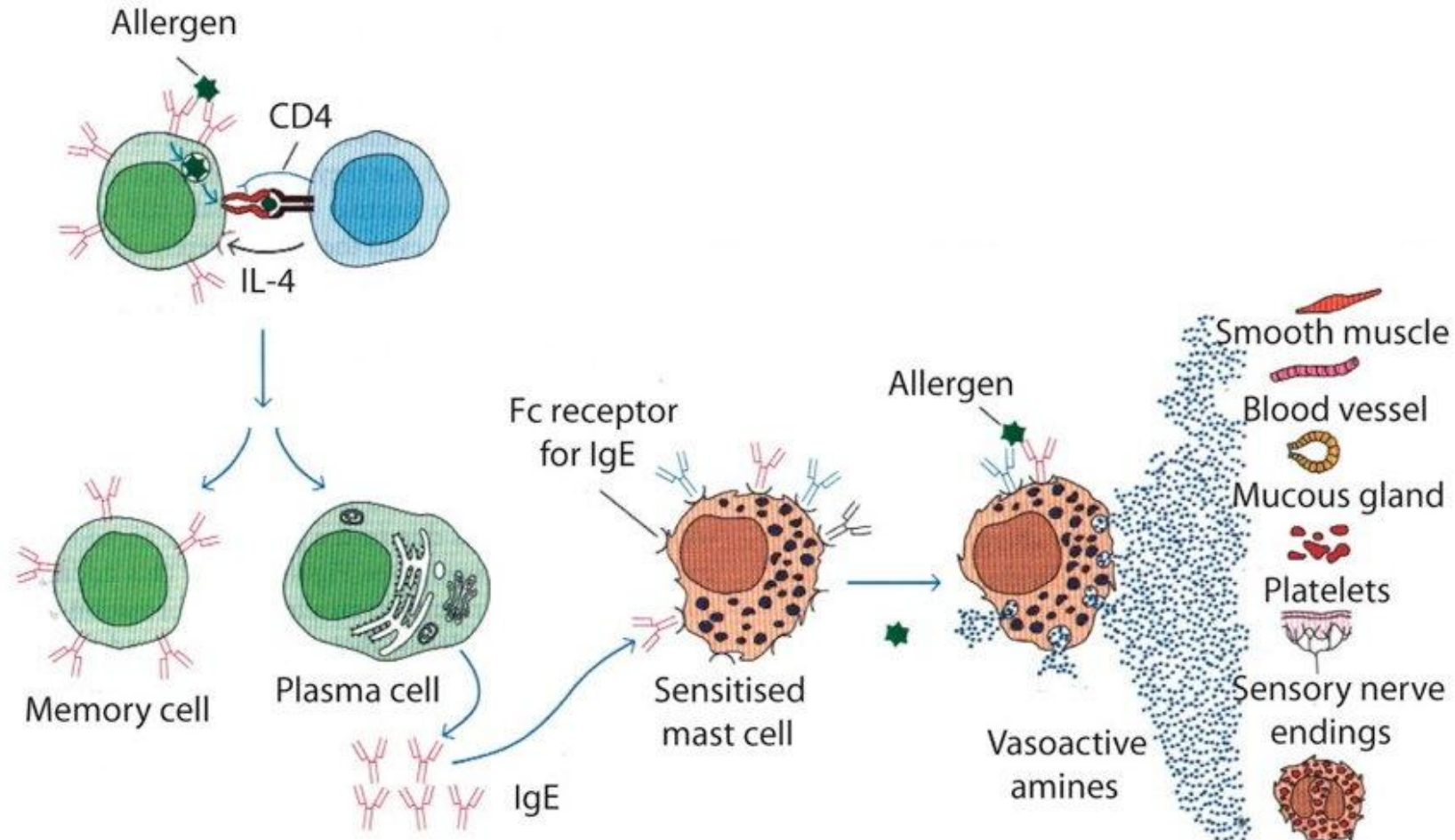
- **Type III reactions are called immuno complex reactions that occur in case of excess of antibody or of antigen (es. some autoimmune diseases and some vasculitis)**

- **Type IV reactions are also called cell-mediated reactions and are due to a lymphocyte response typically directed against self antigens**

Type I – Immediate Hypersensitivity (Allergy)

- Type I reactions occur **few minutes** after the exposure to an allergen in sensitized or atopic individuals
- **Atopy:** the **propensity** of a person to produce IgE antibodies in response to different environmental antigens (**allergens**) and to develop immediate hypersensitivity (**allergic disorders**) Individuals who suffer from enviromental antigen allergies, such as dust or pollen, are called **atopic**
- **Allergens**: antigens that cause an immediate hypersensitivity reaction. Allergens are proteins of pollens, foods, insects venoms, animals (cats, dogs, etc.) or drugs
- These reactions are are due to the **rapid release of pro-inflammatory mediators** by **mast cells and basophils** after the IgE-mediated activation
- In certain patients, immediate reactions **can be followed by late phase** reactions

Type I – Immediate Hypersensitivity (Allergy)



Goldsy RA et al. Immunology 5th Ed, 2003, p 363

Immediate Hypersensitivity Diseases

Clinical Syndromes	Pathological Manifestations
Bronchial asthma	Bronchial hypersensitivity Bronchospasm
Food allergy	Contraction of intestinal smooth muscle
Anaphylaxis	Hypotension Increased vascular permeability Bronchospasm Skin rash
Allergic rhinitis	Sneezing Increased mucosal secretion

Type II – Cytotoxic Reactions

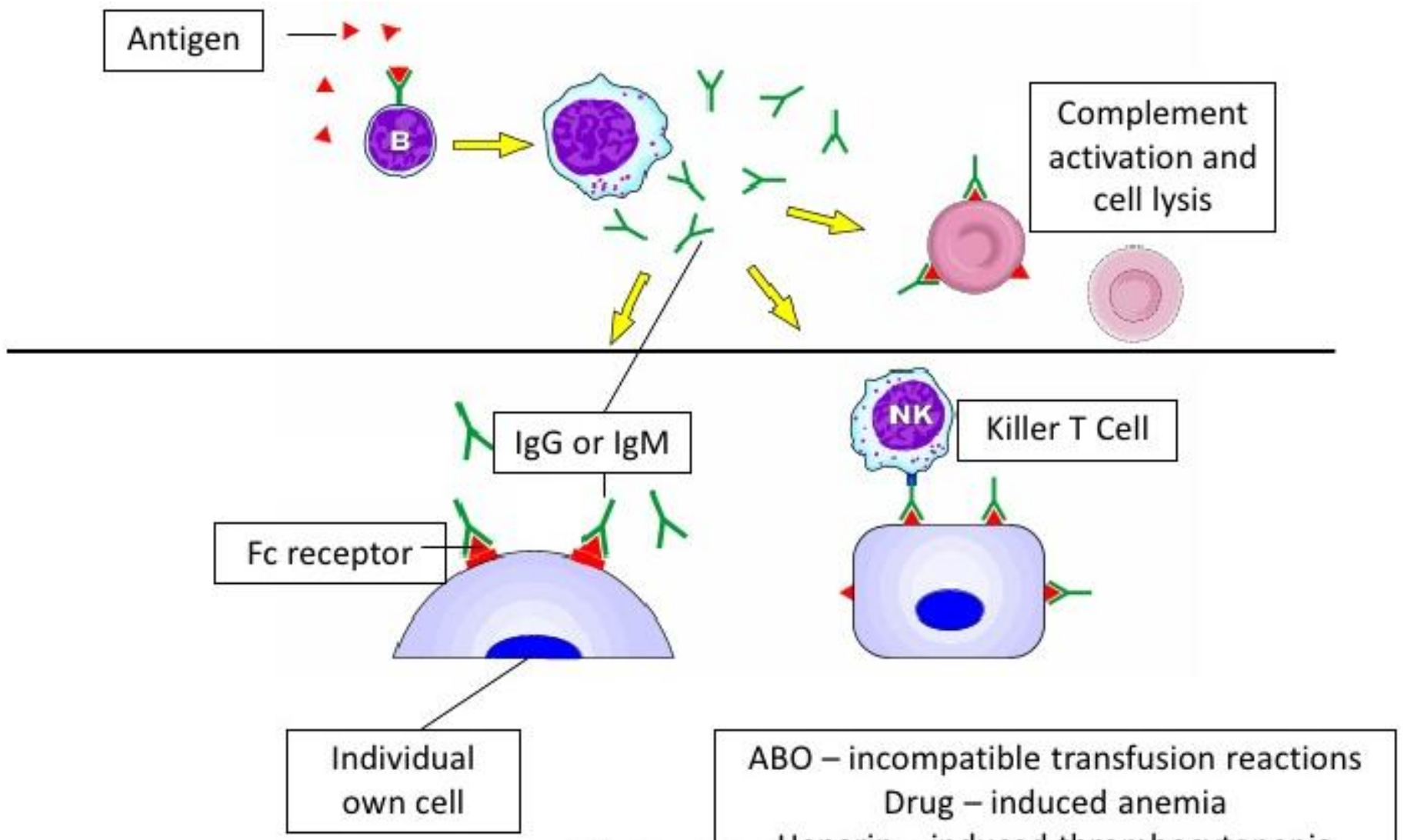
Type II reactions are mediated by antibodies (IgG or IgM) that bind to antigens on the surface of target cells

The antibody interacts with the antigen on the surface of target cell activating the complement that determines cell lysis and thereby a cytotoxic effect

In some cases the cytotoxic reaction is induced by antibodies and is mediated by cytotoxic cells (e.g. NK cells)

Red blood cells and platelets are targets in type II reactions

Type II – Cytotoxic Reactions



Examples of Diseases Caused by Antibodies (Cytotoxic)

Disease	Target Antigen	Mechanism	Manifestations
Autoimmune haemolitic anemia	Rh antigens on red blood cells	Opsonization and phagocytosis of red blood cells	Anemia
Autoimmune thrombocytopenic purpura	Antigens on platelets	Platelet destruction	Haemorrhage
Pemphigus vulgaris	Proteins of the junction of epidermal cells	Gap of junctions of epidermis	Blisters
Graves' disease	Receptor for TSH	Activation of TSH receptor by autoantibodies	Hyperthyroidism
Goodpasture's syndrome	Proteins of basal membrane of alveoli and glomeruli	Inflammation mediated by complement activation and Fc receptors	Glomerulonephritis and alveolar (pulmonary) haemorrhage
Acute Rheumatic Fever	Streptococcus β-haemolitic cross-reactive with type A carbohydrate	Cardiac and valvular inflammation	Arthritis and myocarditis
Myasthenia gravis	Acetylcholine receptor	Inhibition of binding of acetylcholine to its receptor	Muscle weakness

Type III – Immune Complex Reactions

Type III reactions are characterized by immune complex formation that occur in blood or in the basal membranes of the vessels. These reactions damage the tissues in which they occur

The immune complexes are made by antigens in excess, IgG or IgM antibodies and induce complement activation

The immune complexes have particular chemico-physical characteristics that favour their deposition in certain anatomic sites (small blood vessels, renal glomeruli, skin, lung, joints, etc.).

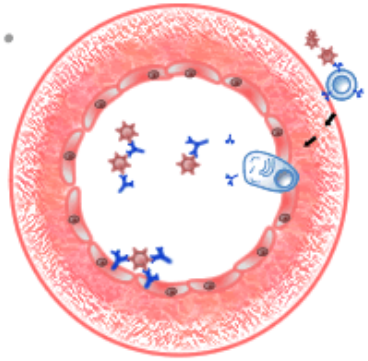
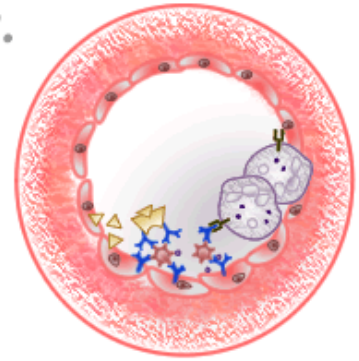
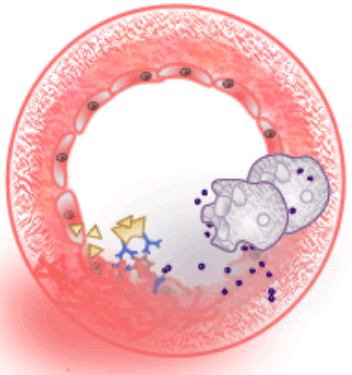
The characteristics of the immune complexes that influence the immune response are:

- **Dimension of complexes: complexes of intermediate or small dimensions are more pathogenic, because big complexes are easier to be phagocitated;**
- **Electric charge of the complex;**
- **Avidity of binding between antigens and antibodies;**
- **Three-dimensional structure of the immune complexes**

Type III – Immune Complex Reactions

Disease	Antigens	Mechanism	Manifestations
Systemic lupud erythematosus (SLE)	DNA, Sm, nucleoproteins	Inflammation mediated by complement and immune complexes	Nephritis, vasculitis, arthritis
Polyarteritis nodosa	Antigen of B virus	Inflammation mediated by complement and immune complexes	Vasculitis
Glomerulonephritis post-streptococcal	Antigens of Streptococci	Inflammation mediated by complement and immune complexes	Nephritis

Type III – Immune Complex Reactions

Formation of the complex	Deposition in tissues	Inflammation
1. 	2. 	3. 
Complexes form and begin to deposit	*Tissue damage begins*	*Diffuse vascular inflammation (vasculitis)*
Immune complexes form when antibodies and antigens in circulation bind to one another. Factors that increase the risk of complexes causing disease include: 1) a large excess of antibody for a particular circulating antigen, 2) persistent complexes, and 3) fast deposition of complexes into tissues. These mechanisms make sense: if the body cannot successfully clear these complexes faster than they are forming or if the complexes persistently deposit in tissues and cause inflammation, pathology can develop. In the above illustration, complexes have formed and a few have begun to deposit.	In the above illustration, the complex has deposited. Several variables influence whether an antigen-antibody complex leads to tissues deposition and disease: - **Size:** larger complexes are cleared faster from circulation than smaller or medium sized complexes; longer-lived complexes have more time to become lodged in tissues - **Ab-Ag affinity:** higher affinity means that the complexes will exist without dissociating for longer and have more time to become lodged in tissues) - **Hemodynamics** of the vascular bed influences the tendency of complexes to cause disease. Favored sites of deposition include the kidney, joints and small blood vessels (high pressure beds).	As you might expect, the main antibody classes that induce this response are those that fix complement or bind to phagocyte Fc receptors (IgG and IgM). These immune complexes activate the complement system, leading to the release of chemical mediators that increase vascular permeability and attract neutrophils and monocytes. The complexes bind Fc receptors on neutrophils and macrophages, activating these cells. Activated cells then try to phagocytize the immune complexes, leading to the release of pro-inflammatory substances, (prostaglandins, vasodilators peptides and chemotactic substances), lysosomal enzymes, (which can degrade basement membrane and extracellular matrix components such as elastin, collagen, cartilage) and reactive oxygen species.

Type IV - Delayed Hypersensitivity

Type IV reactions occur generally within 24-48 hours after exposure to the antigen and for this reason they are considered delayed

The response to the antigen involves always T lymphocytes and for this reason it is defined cell-mediated

Type IV reactions are always characterized by a reaction between antigen, sensitized T lymphocytes and an effector cell (macrophages, eosinophils, etc.)

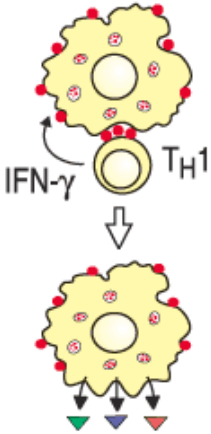
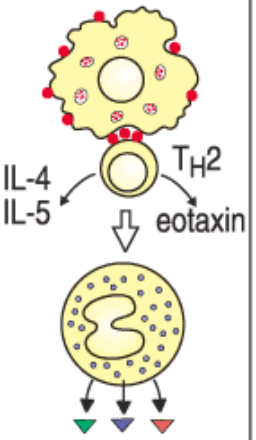
Antigens activate a sensitized T lymphocyte stimulating the production of cytokines, which in turn attract and activate macrophages

If the antigen is not soluble, but is associated with the membrane of a cell, occurs a cytotoxic effect directed by T CD8+ lymphocytes (cytotoxic cell-mediated reactions)

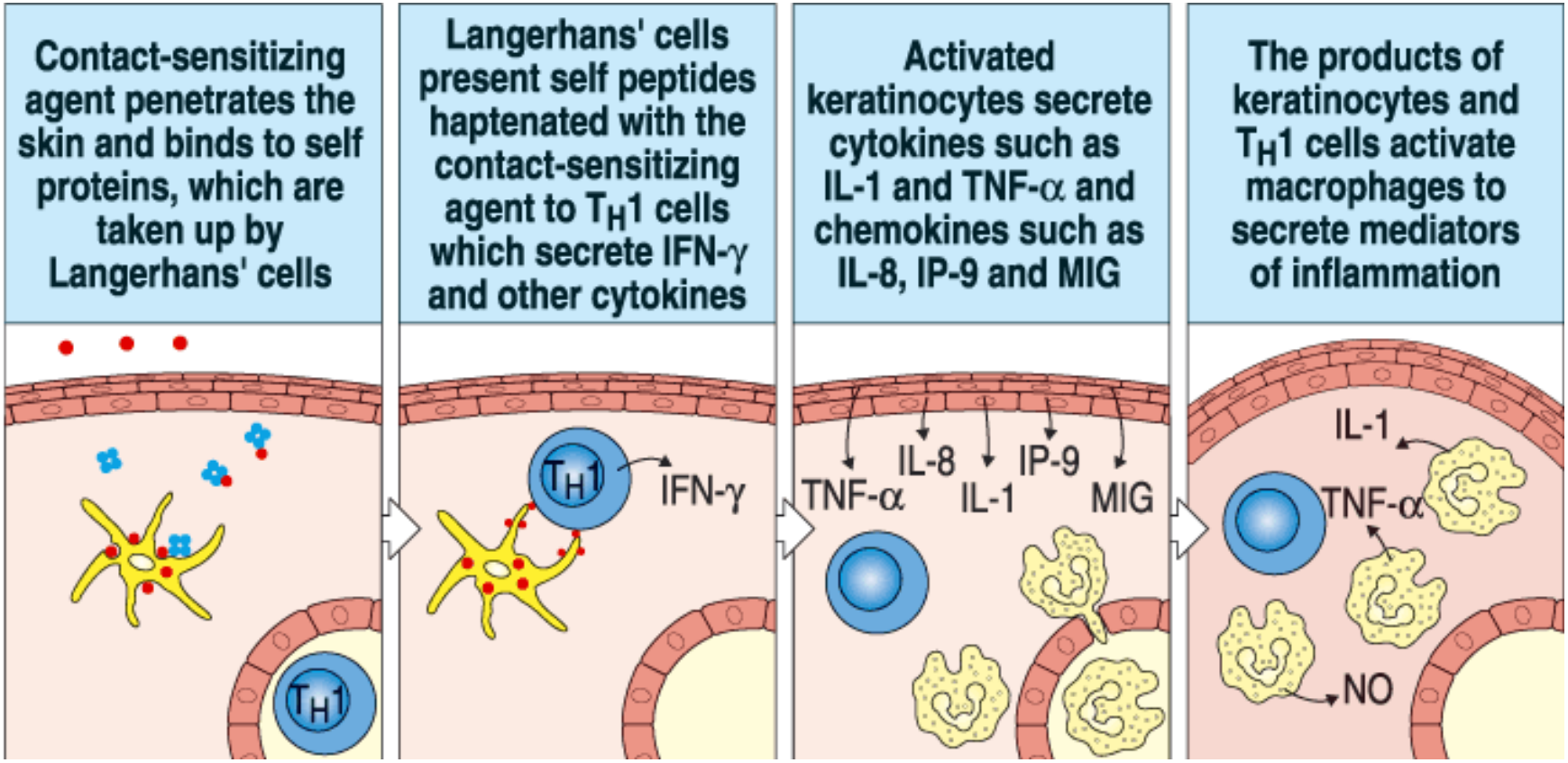
Type IV - Delayed Hypersensitivity

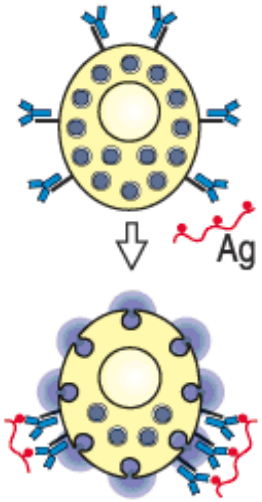
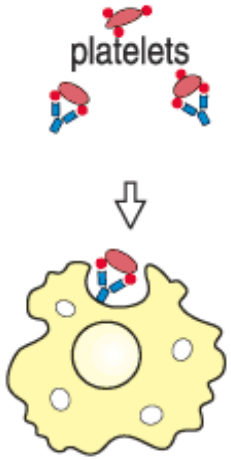
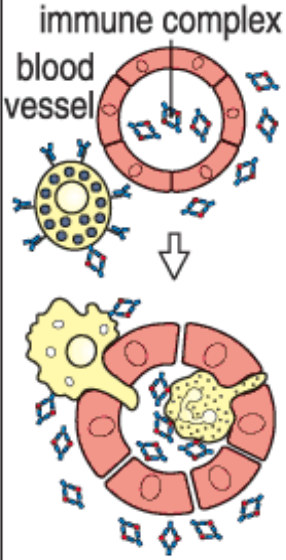
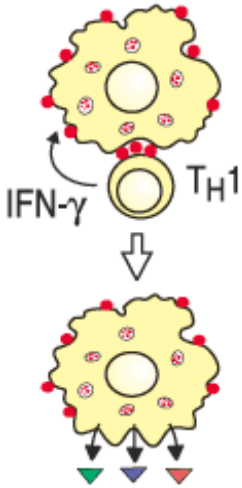
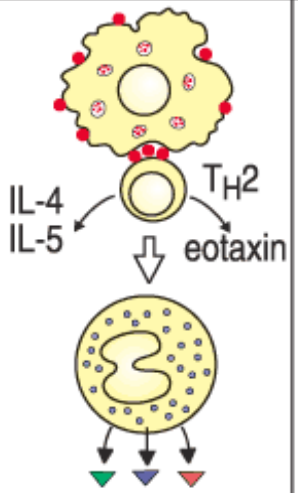
Type IV reactions can be caused by some bacteria such as Tb, Salmonella typhi and Brucella

Sensitized T lymphocytes release cytokines that activate macrophages making them more efficient in phagocytosis against these bacteria

	Type IV		
Immune reactant	T_H1 cells	T_H2 cells	CTL
Antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Macrophage activation	Eosinophil activation	Cytotoxicity
			
Example of hypersensitivity reaction	Contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Contact dermatitis

Type IV - Delayed Hypersensitivity: Contact Dermatitis



	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	Soluble antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	FcR^+ cells (phagocytes, NK cells)	FcR^+ cells Complement	Macrophage activation	Eosinophil activation	Cytotoxicity
						
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (e.g., penicillin)	Serum sickness, Arthus reaction	Contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Contact dermatitis