MED437
KING SAUD UNIVERSITY

IMMUNOLOGY
TEAM 437

Immunology

Teamwork 437

Lecture **(5)**: Hypersensitivity Reactions

Color index:
IMPORTANT
Definition
Explanations + notes
Extra (or gray)

Objectives

- To know that hypersensitivity reactions are over and excessive immune responses that can be harmful to the body in four different ways.
- To be familiar with inflammatory processes in Type I hypersensitivity reaction that mediates allergic inflammation.
- To recognize that Type II hypersensitivity deals with immune responses against antigens that are integral part of cell membrane and are usually associated with autoimmune disorders.
- To know that Type III hypersensitivity reactions are mediated by immune complexes and cause vasculitis.
- To describe Type IV hypersensitivity is a purely cell mediated immune response associated with chronic inflammation.

Reference
Kuby Immunology 7th Edition 2013
Chapter 15 Pages 485-510

Note: there are some explanatory videos on some pictures

What is hypersensitivity?

- **Protective immunity**: desirable reaction
- **Hypersensitivity**: undesirable reaction
- Undesirable responses can be mediated by:

Antibody-Antigen binding: (Types I-III)

Cell-mediated reaction (Type IIII)

Types of Hypersensitivity

Type I: Immediate Hypersensitivity

- Anaphylactic reactions (allergies)
- Caused by allergens (non-infectious foreign bodies)

Gel & Coombs Classification:
- Ig Ab

Composed of:
- Sensitization phase
- Challenge phase

Type II: Cytotoxic Hypersensitivity

- Anti-body mediated destruction of healthy cells
- These antibodies are tissue specific

Gel & Coombs Classification:
IgG to tissue antigens

Involves activation of complement proteins

Type III: Immune Complex Hypersensitivity

- Antibody reacts with soluble antigen to produce immune complex
- Immune complex deposited in many types of tissues cause inflammation

Gel & Coombs Classification:
- Ig immune complexes

Type IV: Delayed Hypersensitivity

- Cell mediated immunity
- Formation of abnormal tissue (Granuloma)

Gel & Coombs Classification:
Cell mediated (T_{helper} & $T_{cytotoxic}$)

Composed of:
- Sensitization phase
- Challenge phase

Type I: Immediate Hypersensitivity

Features

- Allergic reaction
- Anaphylactic reactions: severe & rapid forming systemic forms (life threatening)

- Most people won't react to these allergens
- "Atopic individuals" respond by producing increased amounts of IgE
- Non-allergic individuals respond by producing IgG

Components of Type I

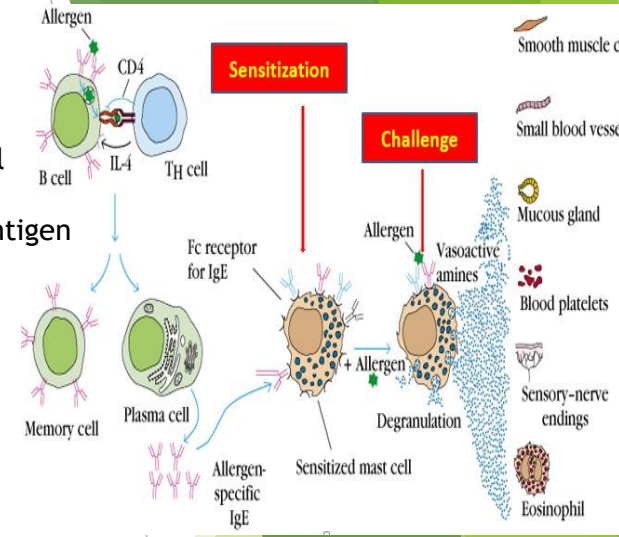
- Anti-body: IgE
- Cellular components: Mast cells, Basophils, Eosinophils
- Antigens: Allergens: non-infectious agents that produce immune response; Low-molecular weight; Soluble

Allergens:
- Dust mite
- Pollen
- Animal dander
- Shellfish
- Nuts
- Drugs

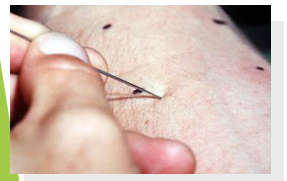
Mechanism

Sensitization phase:
→ Allergen binds to B lymphocyte (APC)
→ B lymphocyte presents allergen to T_{helper} cell
→ Activation to Plasma cell
→ Production of anti-bodies (IgE) specific to antigen
→ Anti-bodies bind on surface of mast cells

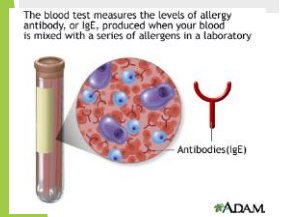
2. Challenge phase:
→ Second exposure to allergen
→ Allergen binds with antibodies on mast cells
→ Mast cells stimulated to release histamine
→ Anaphylactic reaction (Allergy)
→ Results in many physiological changes



Diagnosis



Skin-prick test:
- Prick skin with small sample of allergen
- Patients who are hypersensitive will develop rash & urticarial (immune response)



RAST(Radioallergosorbent test)
- Specific IgE measurement
- Measure amount of IgE antibodies which increase with allergies

Elimination/provocation test
- Method to test out food tolerance
- Used to identify food allergies

Anaphylactic reaction:

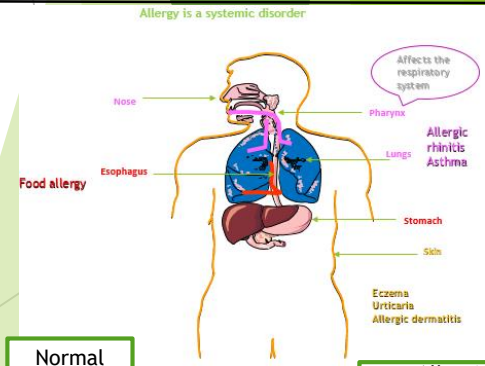
Severe Type I reaction
Exposure to allergen
IgE mediated

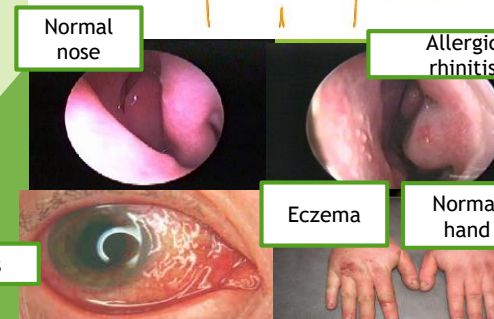
Example: Hymenoptera (bee/wasp)
sting antigen
→Enters blood stream
→System inflammation
Life threatening

Clinical examples

Anaphylactoid reaction:

- Non-IgE mediated reaction
- Produces same clinical expressions and symptoms of anaphylaxis
- Caused by contrast media/local anesthetics
- Results in direct degranulation of mast cells
- NO sensitization/challenge phase or synthesis of antibodies

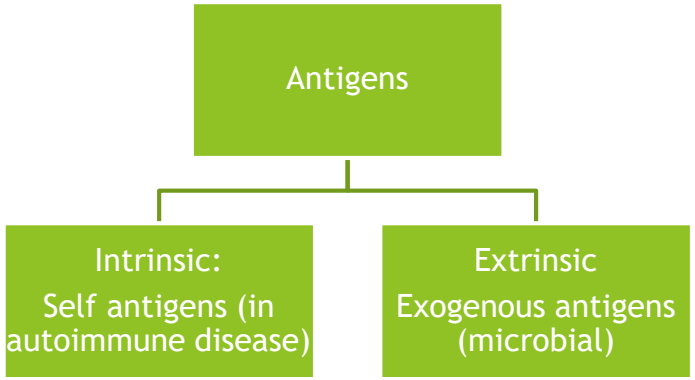




Type II: Cytotoxic Hypersensitivity

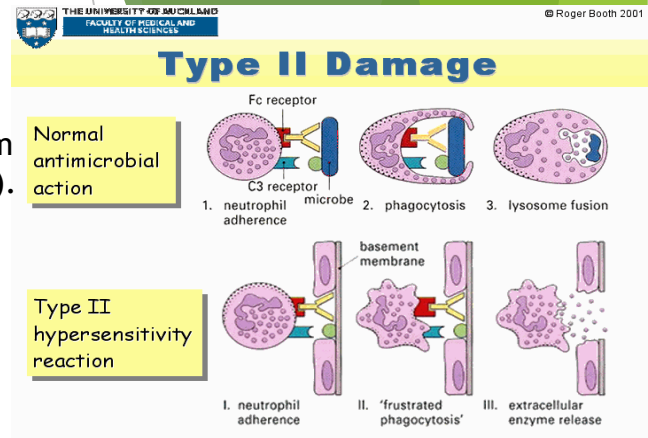
Features

- Antibodies bind to antigens on tissue surface.
- IgG mediated process.
- Involves activation of complement protein system.

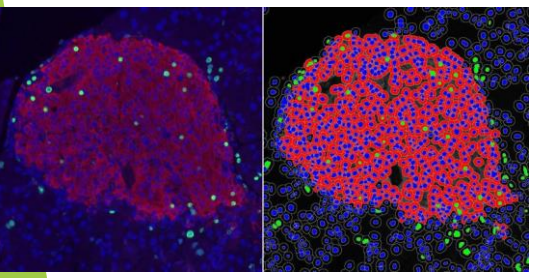


Mechanism

1. Antibody (IgG) binds to antigen on cell membrane surface.
2. Activation of compliment protein system via classical pathway (antigen-antibody).
3. Result: Opsonization of antigen and chemotaxis of macrophages.
4. Frustrated phagocytosis resulting in some cell damage.

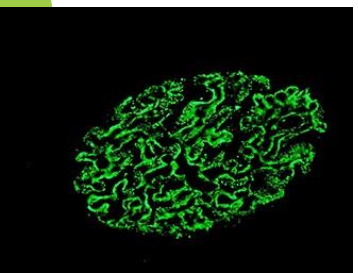


Diagnosis

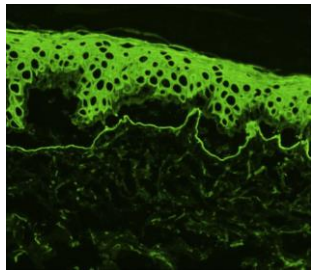


Detection of antibodies and antigens by Immunofluorescence in tissue biopsy specimen

Example:



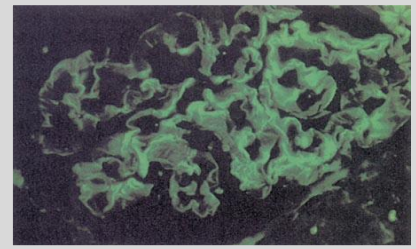
→Kidney



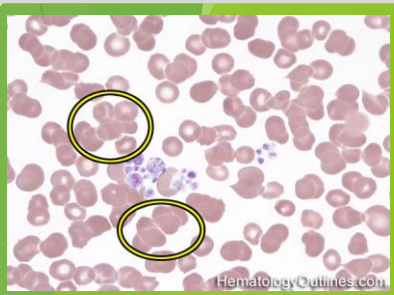
→Skin

Clinical examples

1. Glomerulonephritis
caused by
Anti-Glomerular Basement membrane disease
Antibodies directly attack and bind to antigens on cell surface resulting in frustrated phagocytosis and cell damage



2. Mismatched blood transfusion:
Results of agglutination (clumping) of donor's red blood cells by antibodies of recipient
Ultimately leads to hemolysis of donor RBCs



Type III: Immune Complex Hypersensitivity

Features

Features:

Antibody (IgG or IgM) + Antigen (soluble)

- Immune – Complex formation

- Complement activation (classical pathway)

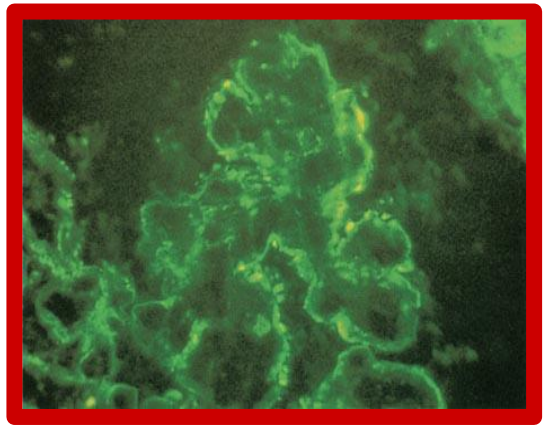
- Attraction of inflammatory cells

Mechanism

- When an antigen reacts with an antibody the product they form is called an immune complex which is capable of inducing an inflammatory response
- Immune complexes are deposited in tissues like kidneys (nephritis), joints (arthritis) or blood vessels (vasculitis)
- Antibodies attach to soluble antigens as opposed to antigens on cell surfaces (as seen in type 2 hypersensitivity).

Diagnosis

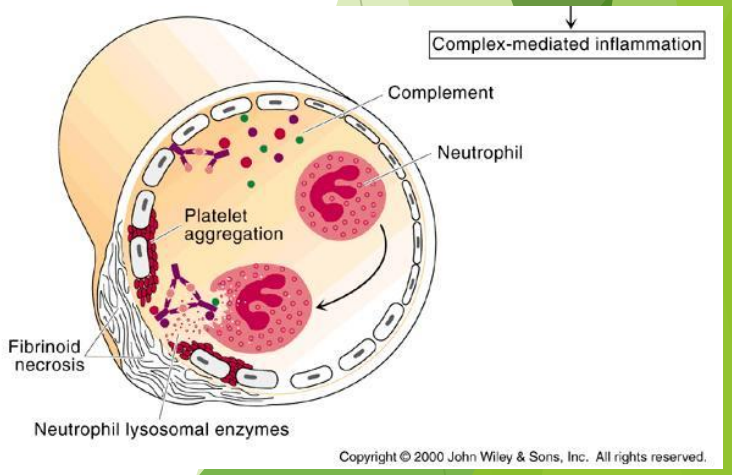
Demonstration of specific immune complexes in the blood or tissues by: Immunofluorescence



Clinical examples

Clinical examples:

- Glomerulonephritis: Rheumatoid arthritis, SLE
- Happened as consequences of deposition of the free antigen.
- Systemic Lupus Erythematosus



Fibrinoid necrosis caused by type III hypersensitivity

Type IV: Delayed Hypersensitivity

Features

Features :

- Cell mediated immune response

- Antigen dependent T cell (CD4 generally and CD8 occasionally) activation via MHC Class I (for CD8) or Class II (for CD4)
- Activated macrophages
- Delayed onset (2-4 days)

(this`s why we call it Delayed Hypersensitivity)

Abnormal cellular response

-(Granuloma formation)

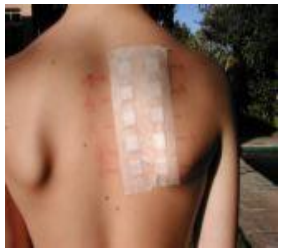
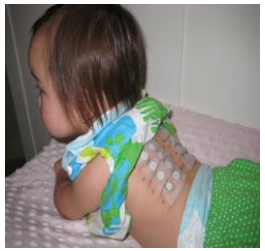
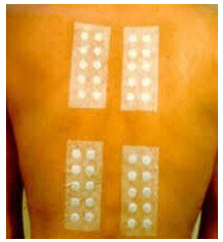
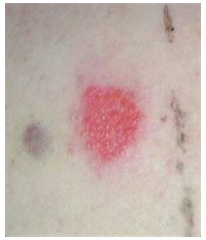
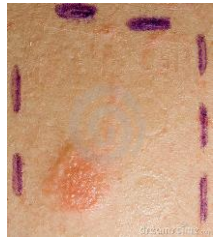
Mechanism

- **Sensitization phase:**
  - 1-2 week period
  - (production of delayed hypersensitivity T lymphocyte that recognizing that antigen)
- **Effector phase:**
  - 24-72 hours
  - Effector cells
  - (activated macs)
  - act non-specifically

Diagnosis

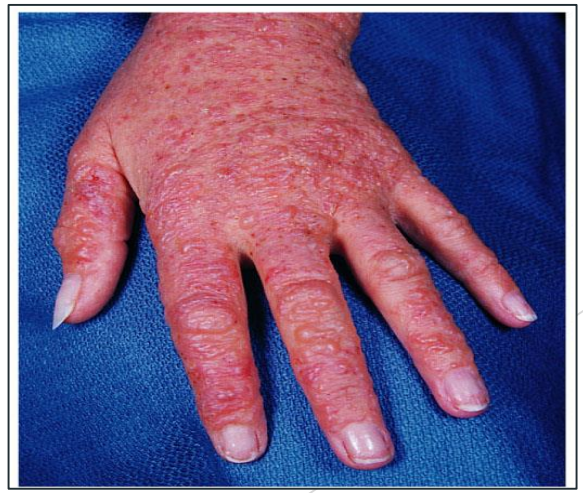
1. Delayed skin test (Mantoux test)
2. Patch test (Contact dermatitis)
3. Lymphocyte transformation test

2. Patch test (Contact dermatitis)

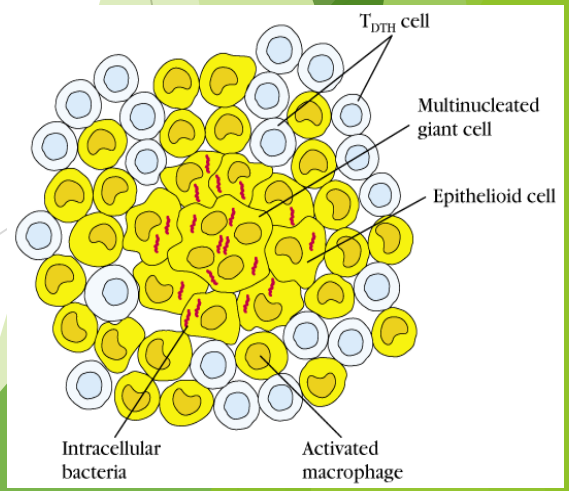
Clinical examples

- Contact dermatitis



- TB granuloma

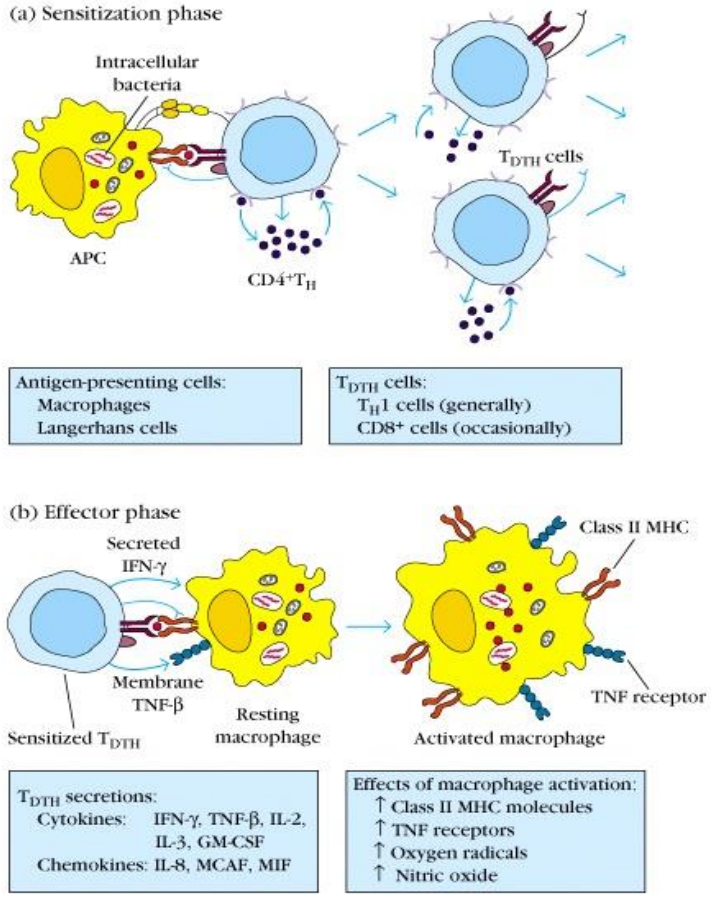
(persistent antigen)



Development of DTH Response:

- Depends on APC :
- If it is class I (Cytotoxic T cell)
- If it is class II (T helper cell)

*الصورة مهمة



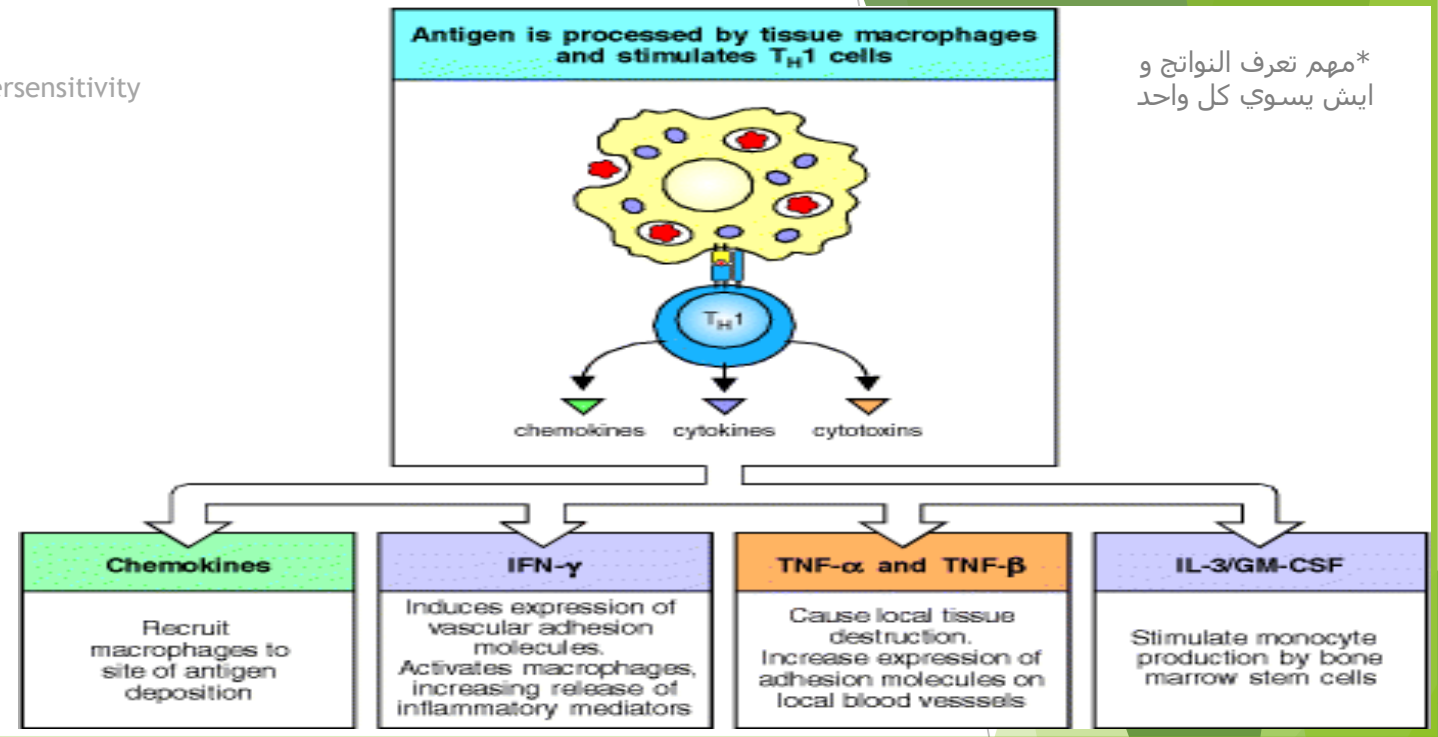
Mediators released by T_{DTH} cells:

↓

Delayed type Hypersensitivity

INF: Interferon
TNF : tumor necrosis factor
IL: Interleukin
GM-CSF: Granulocyte-macrophage colony-stimulating factor

*مهم تعرف النواتج و ايش يسوي كل واحد



Pathophysiology of Contact dermatitis:

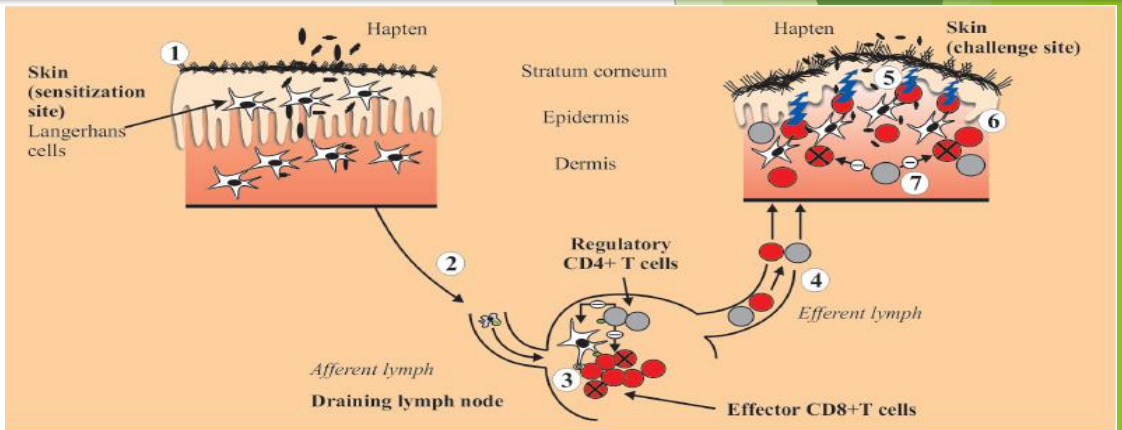


FIGURE 1: **Pathophysiology of allergic contact dermatitis**
Sensitization phase (afferent phase). Haptens penetrate the epidermis (step 1) and are uptaken by epidermal cells including skin DC which migrate to the draining lymph nodes (step 2) where they present haptenated peptides to both CD8+ effector T cells and down-regulatory CD4+ T cells (step 3). Specific T cell precursors clonally expand in draining lymph nodes, recirculate via the blood and migrate to tissues including the skin (step 4).
Elicitation phase (challenge phase, efferent phase). When the same hapten is applied on the skin, it is uptaken by epidermal cells, including skin DC and keratinocytes (step 5) which present haptenated peptides to specific T cells. Activation of CD8+ CTLs induces apoptosis of keratinocytes and production of cytokines and chemokines by skin resident cells (step 6). This leads to the recruitment of leucocytes from the blood to the skin. CD4+ T cells may block activation/expansion of CD8+ effectors in lymph nodes during sensitization and in the skin during the elicitation phase of CHS (step 3 and 7).

Test your knowledge!

- 1- Which type of Hypersensitivity includes cell mediated reaction?
- A. I B. II C. III D. IV

- 2- Which type of Hypersensitivity responds by producing large amounts of IgE?
- A. I B. II C. III D. IV

- 3- Which of the following is not a cellular component of type I hypersensitivity?
- A. Mast cells B. Basophils C. Eosinophils D. Neutrophils

- 4- Anaphylactic reactions are considered in _____
- A. Type I hypersensitivity B. Type II hypersensitivity C. Type III hypersensitivity D. Type IV hypersensitivity

- 5- Immunofluorescence can be used to diagnose which type of hypersensitivity?
- A. I B. II C. III D. B&C

- 6- Which type of Hypersensitivity can cause fibrinoid necrosis?
- A. I B. II C. III D. IV

- 7- Allergic dermatitis is caused by?
- A. I B. II C. III D. IV

- 8- Contact dermatitis is caused by?
- A. I B. II C. III D. IV

- 9- Rheumatoid arthritis is a clinical example of?
- A. I B. II C. III D. IV

- 10- Immediate Hypersensitivity is which type of hypersensitivity?
- A. I B. II C. III D. IV

Answers: 1D 2A 3D 4A 5D 6C 7A 8D 9C 10A

Team members

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