Foundation block

Hypersensitivity

Lecture 6

432 immunology team

Objectives:

- ☒ **To know that hypersensitivity reactions are over and excessive immune responses that can be harmful to body in four different ways**

- ☒ **To be familiar with inflammatory processes in Type I hypersensitivity reaction that mediate allergic inflammation**

- ☒ **Recognize that Type II hypersensitivity deals with immune responses against antigens that are integral part of cell membrane and are usually associated with autoimmune**

- ☒ **To know that Type III hypersensitivity reactions are mediated by immune complexes and cause vasculitis**

- ☒ **Describe Type IV hypersensitivity is a purely cell mediated immune response associated with chronic inflammation**

Note:

Black: slides

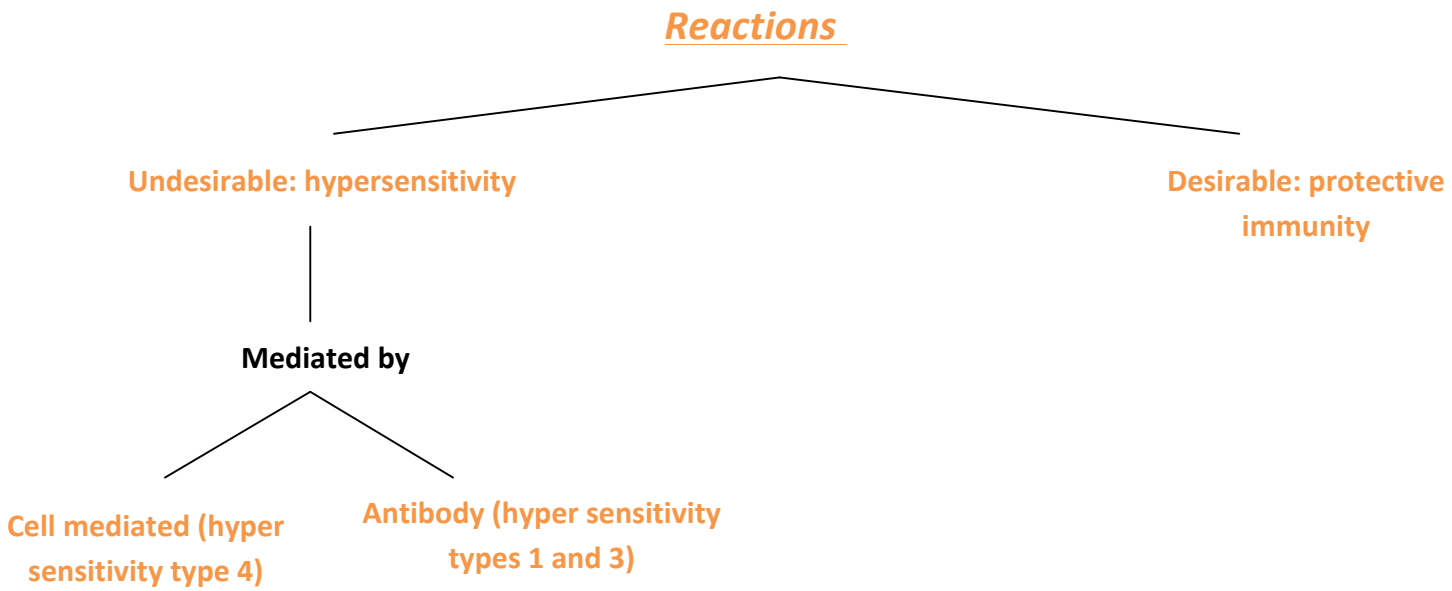
Orange: Explanation

Purple: Extra

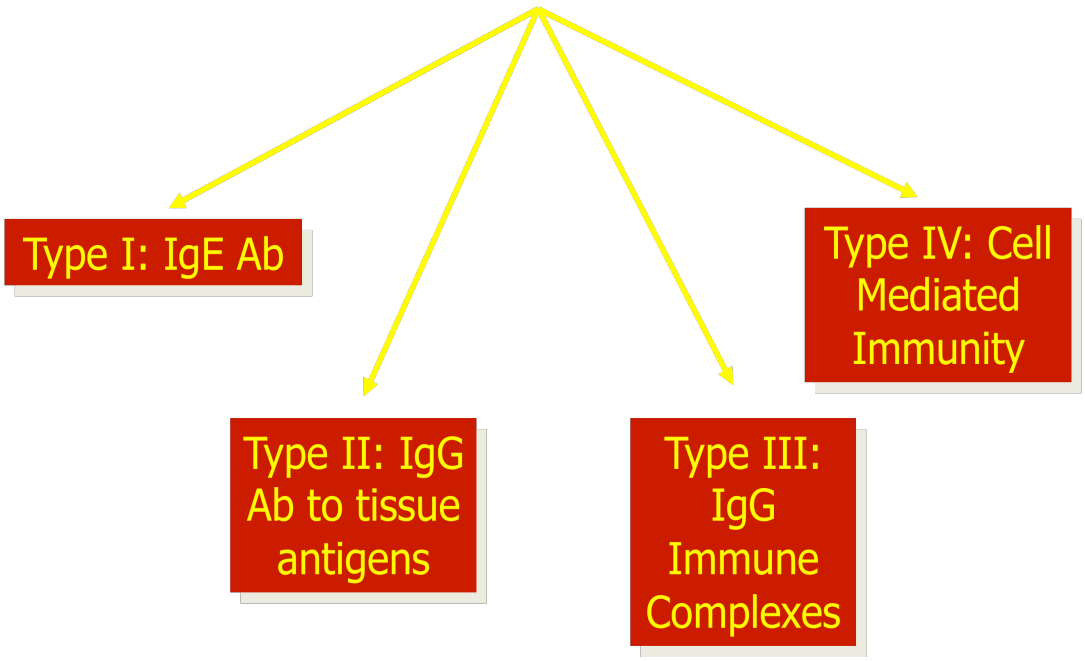
Red: Important

What is hypersensitivity?

- Protective immunity: desirable reaction.
- Hypersensitivity: undesirable reaction.
- **Undesirable responses can be mediated by**
  - **Antibody binding** to antigens (Types I-III)
  - ***Cell mediated reaction*** to chemicals or proteins (Type IV)



Gel and Coombs Classification



Type 1: **antibody mediated, IgE**.

Type 2: **antibody mediated, IgG, tissue antigens (not free antigens)**.

Type 3: **antibody mediated, IgG**. (Immune complex means antigen + antibody)

Type 4: **cell mediated.**

Type I: Immediate Hypersensitivity (antibody mediated):

- Most people will not react to these allergens but some individuals "***atopic***" respond by producing large amounts of IgE.

- Non-allergic individuals respond to these allergens by producing IgG antibodies

- Type I is termed as:
  - Immediate Hypersensitivity
  - Anaphylactic reactions (Exaggerated allergic reaction to a foreign protein resulting from previous exposure to it and they are related to IgE).
  - Allergic reactions
    (Occurs within minutes to hours)

- Features:
  - Antibody type ⟶ IgE
  - Cellular components ⟶ Mast cells, basophiles & eosinophil (They are important because they have IgE receptors).

- Antigens ⟶ low molecular weight & highly soluble (also known as allergens).

Allergens

Some of the allergens involved in type I hypersensitivity are: pollens, dust mite allergen (image below), animal dander, nuts, shellfish, various drugs ..etc. (Also some other food allergies).

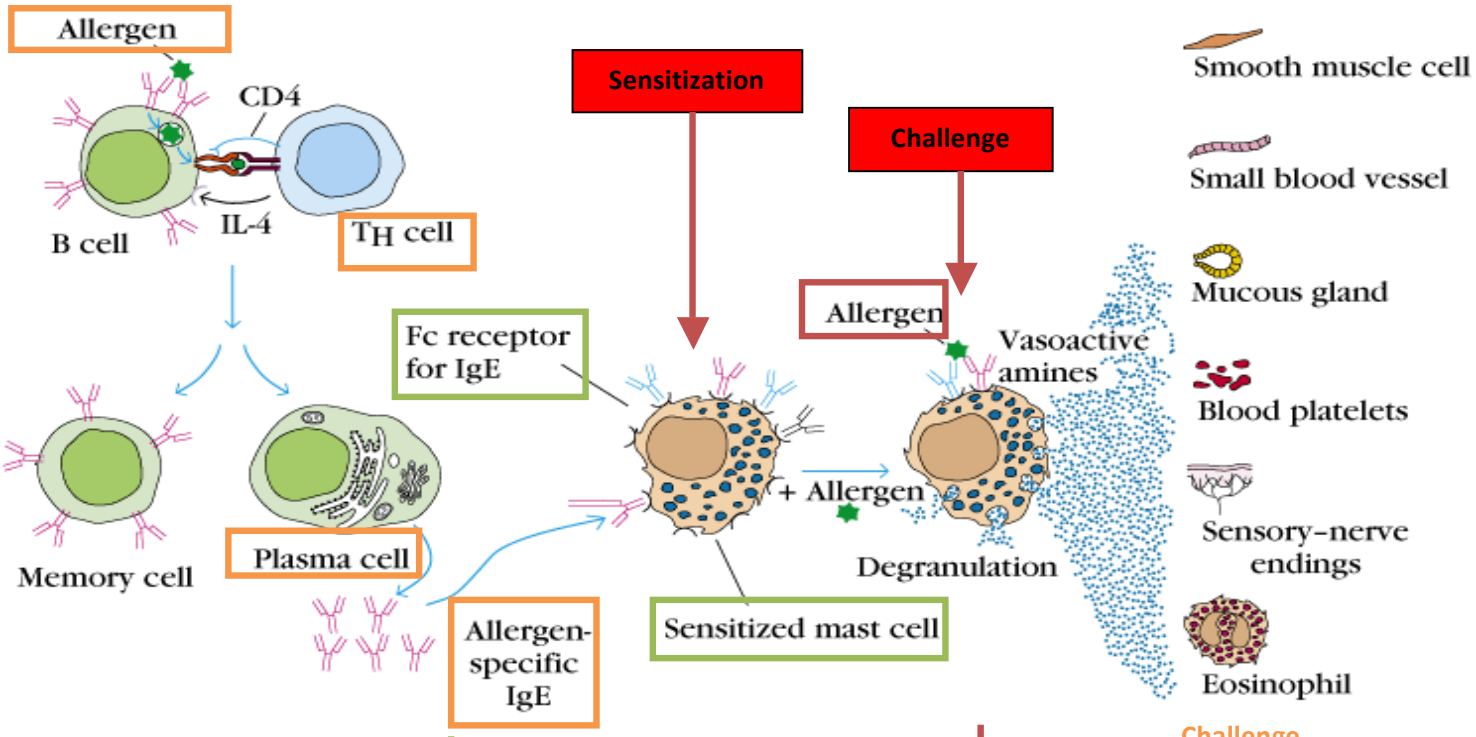
Type I reactions occur in two phases

■ Sensitization phase

First contact with allergens

■ Challenge phase

Subsequent contact with allergens.



1 Allergen binds to B cell (antigen presenting cell)

2 B cells then interacts with T helper cell (T will help B cells produce plasma cells)

3 plasma cells produce allergen specific antibodies.

T helper cells help B cells produce plasma cells leading to the production of allergen specific antibodies

Sensitization phase

1. Mast cells express high affinity receptors for igE (Fc receptor for IgE)

2. Fc receptor will interact with specific antibody IgE

3 .now the cell is sensitized

The cell is sensitized when a specific anti body binds to the Fc receptor

Challenge

1. After the mast cell is sensitized the allergen will bind to that cell.

2. This will lead to the biological activity of the mast cell leading to the production of their mediators (the mediators will cause sneezing, itching, other allergic reactions.

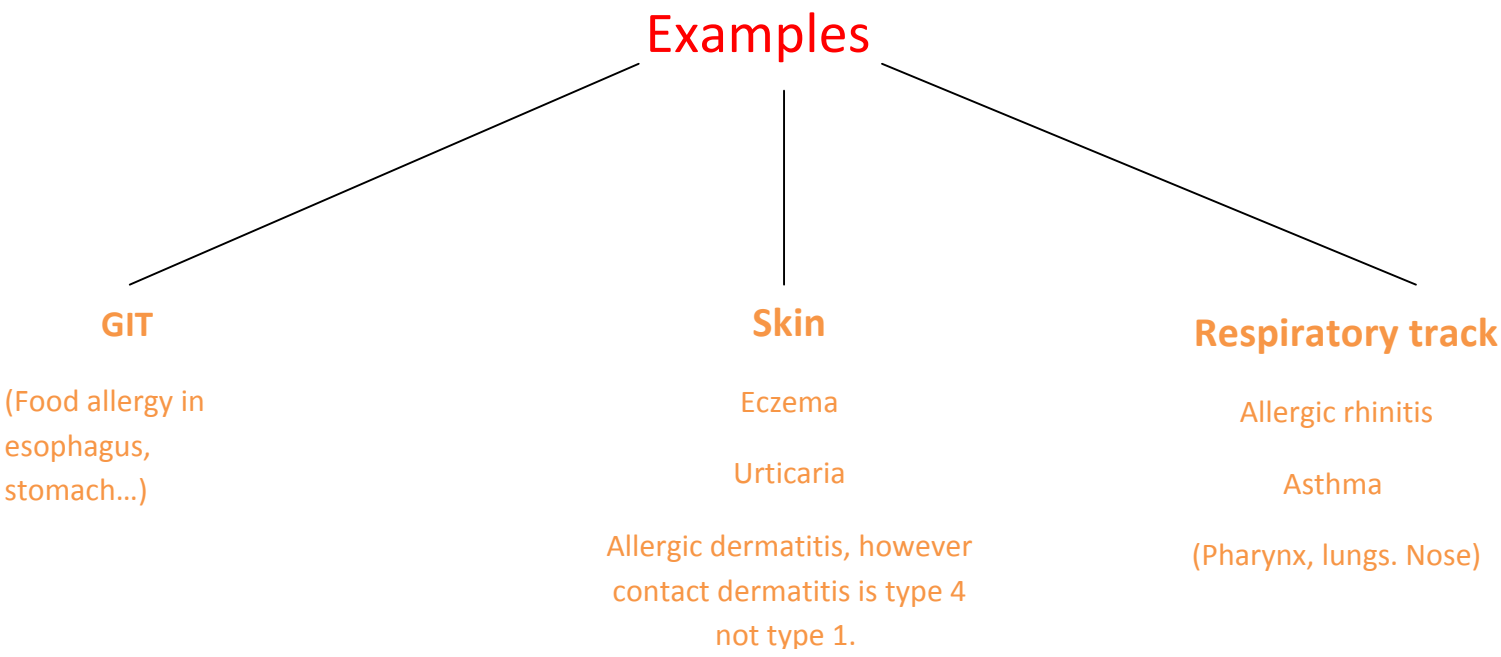
The allergen will bind to the mast cell leading to biological activity, Histamine is produced.

Primary and secondary mediators:

الدكتور ركز على الهستامين

Mediator	Effects
PRIMARY	
Histamine, heparin	Increased vascular permeability; smooth-muscle contraction
Serotonin	Increased vascular permeability; smooth-muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A)	Neutrophil chemotaxis
Proteases	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-2, IL-3, IL-4, IL-5, IL-6, TGF-β, and GM-CSF	Various effects (see Table 12-1)

Allergy is a systemic disorder



Injected allergens:

Example: The bee sting

Bee sting venom enters the blood stream

→ Systemic inflammation

→ Anaphylactic shock

(Life threatening) also black ants can cause anaphylactic shock.

Anaphylactic shocks:

- **Anaphylactic shock: A widespread and very serious allergic reaction. Symptoms include dizziness, loss of consciousness, labored breathing, swelling of the tongue and breathing tubes, blueness of the skin, low blood pressure, heart failure, and death. Immediate emergency treatment is required for this type of shock, including administration of antivenom in the case of bee or wasp stings.**

-In the cases of muscle contraction they usually use epinephrine pen kind of needle that contains adrenaline, which will decrease muscle contraction rate and prevent trachea from closing.

-Anaphylactoid reactions are similar to anaphylactic shock but not the same, anaphylactoid shock is not related to IgE.

Diagnosis of Allergy

1. Skin prick test (SPT)
2. Specific IgE measurement (RAST)
3. Elimination / Provocation test (Food allergy)
4. Intradermal test in labs for food or environmental allergy.

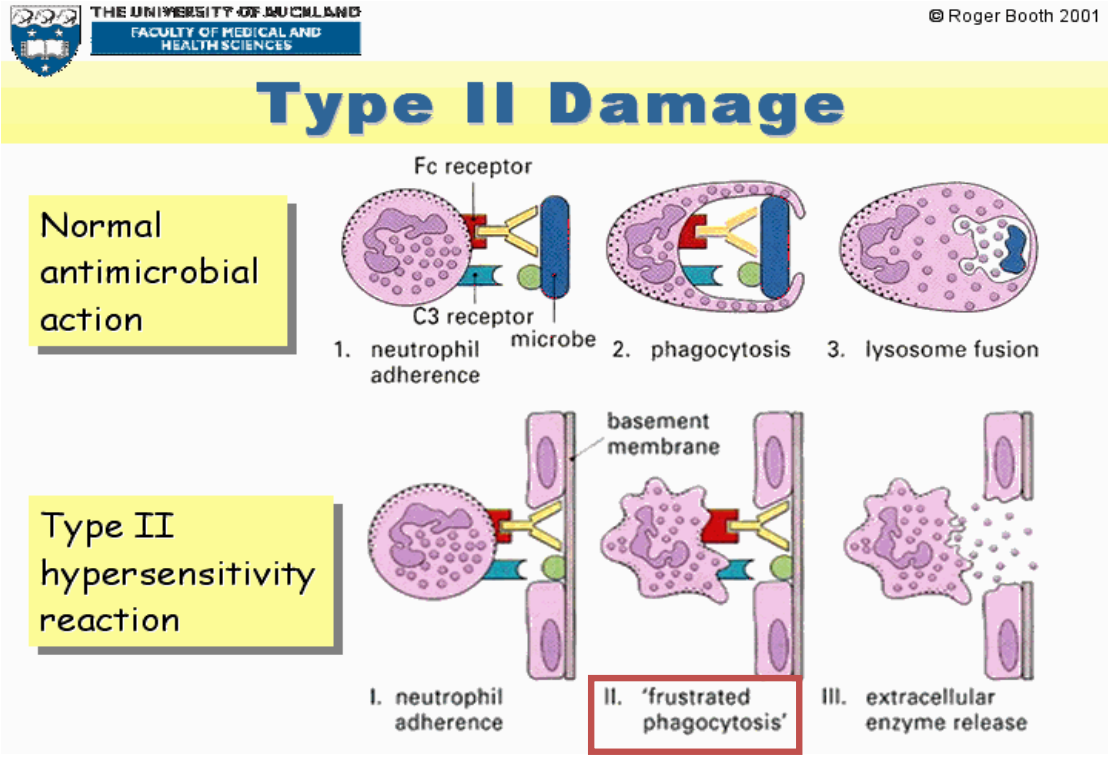
Figure 15-10
Kuby IMMUNOLOGY, Sixth Edition

SPT

Type II Hypersensitivity Reactions (antibody mediated)

Features:

- Antibody type ⟶ IgG (mainly) (or IgM)
- Antigens ⟶ bound to cell membrane (Self antigens) (not free)
- Exogenous antigens (microbial)
- Complement activation (Invariable)



Biological activity (sneezing, itching…)

Clinical examples:

Glomerulonephritis (anti-glomerular basement membrane) (activation of the inflammatory cells like neutrophils in the basement membrane which contains ABs)

Mismatched blood transfusion

(The target??) The RBCs of the donor are the target (destruction of the cellular antigen on the RBC wall by antibodies)

Diagnosis

- Detection of antibodies and antigens by **Immunofluoresence** in tissue biopsy specimens e.g. kidney, skin etc.

Type III: Immune Complex Hypersensitivity

*Antigen reacting with Antibody (Free) is called immune complex.

* An immune complex can induce inflammatory response

* Immune complexes are deposited in the tissues like:

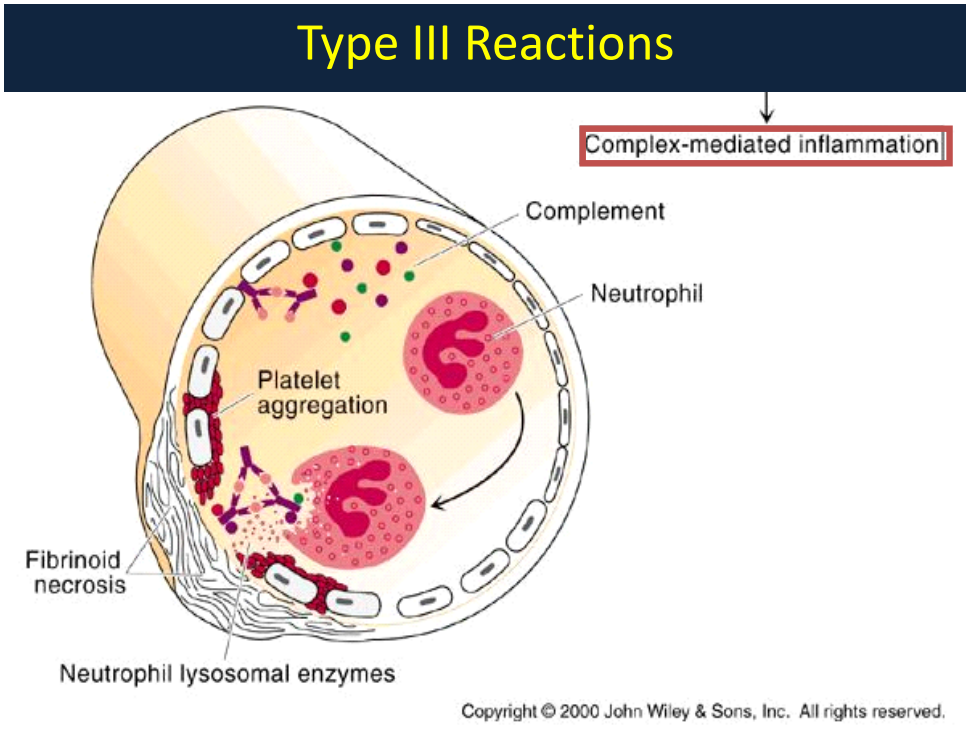
1- Kidneys (Nephritis)

2- Blood (Vasculitis)

3- Joints (Arthritis)

Features:

Antibody is IgG (Mainly)/IgM + Antigen (soluble) → immune complex → complement activation → inflammatory response.



Clinical Applications:

1- Glomerulonephritis (deposit in blood Vessel Wall different than type 2 glomerulonephritis which deals with anti-glomerular cell membrane)

2- Rheumatoid Arthritis 3-Drug eruption

Diagnoses:

By **Immunofluorescence**.

Type IV Hypersensitivity reactions

(Delayed hypersensitivity)

Features:

1- CELL MEDEIATED IMMUNE RESPONSE

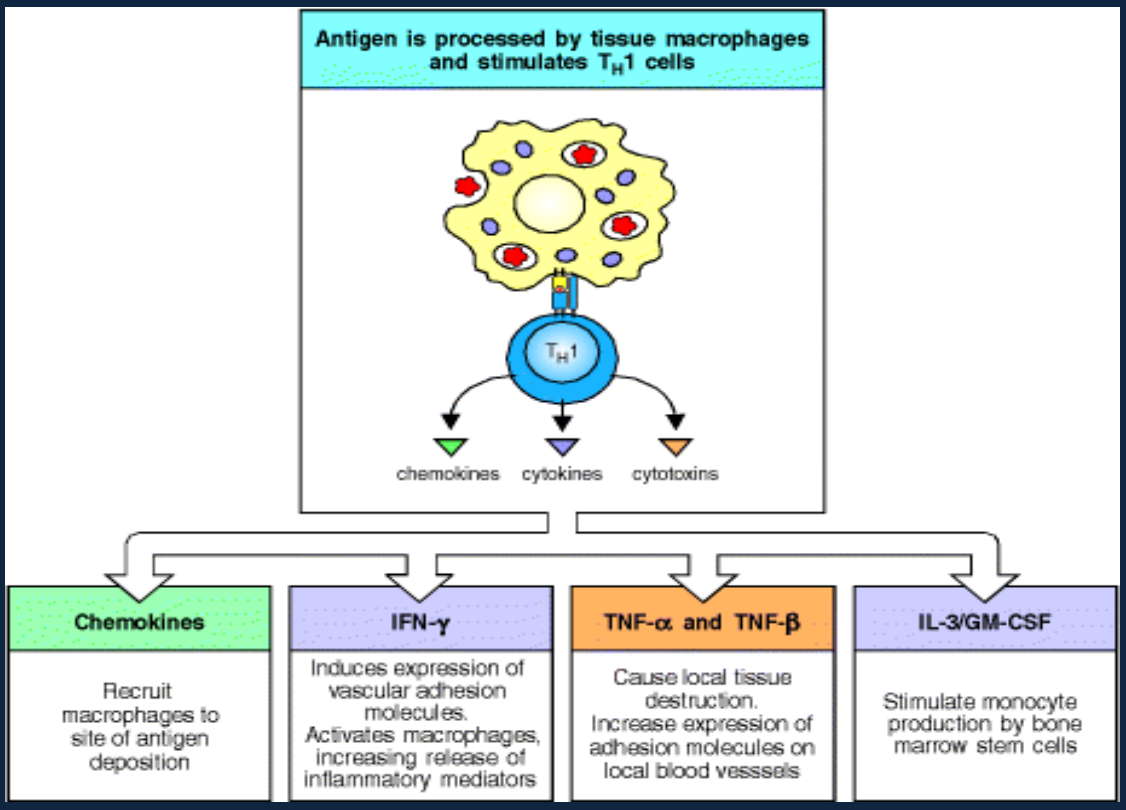
2- ANTIGEN: CD4 helper cells (Generally) (note that we will be using TH1 (the inflammatory helper cells) not TH2 (because we have nothing to do with Antibodies), CD8 cytotoxic cells (Occasionally) activation is going to be via MHC class 1 (CD48) and 2 (CD4).

3- Activated macrophages very important because release a lot of mediators.

4- Delayed onset (2-4 days)

5- Abnormal cellular response (GRANULOMA FORMATION like in TB)

Mediators released by T_{DTH} cells



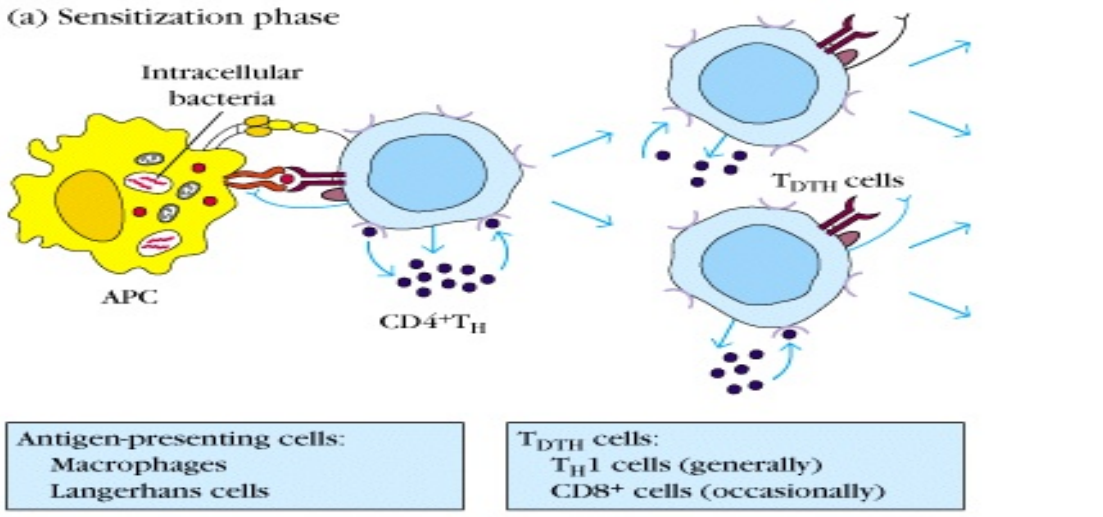
* DTH = Delayed type hypersensitivity.
*Stimulates T h1 Cells to release Chemokine, Cytokines, Cytotoxins.

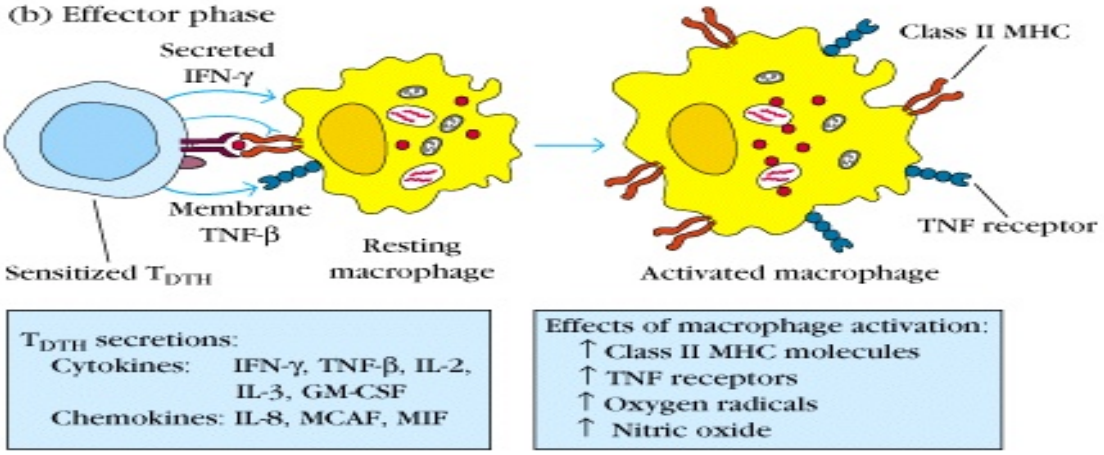
Development of DTH response:

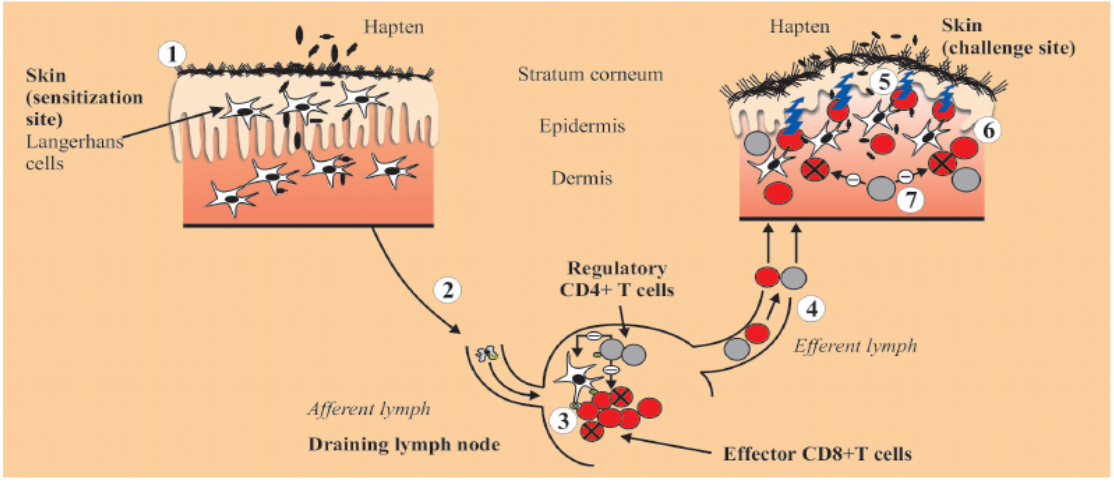
*Sensitization phase takes from 1-2 weeks

* Effector phase take from day - 3 days

Activated Macrophages (effector cells) are nonspecific


(a) Sensitization phase
Intracellular bacteria
APC
CD4+TH
TDTH cells
Antigen-presenting cells:
Macrophages
Langerhans cells
TDTH cells:
TH1 cells (generally)
CD8+ cells (occasionally)


(b) Effector phase
Secreted IFN-γ
Membrane TNF-β
Sensitized TDTH
Resting macrophage
Class II MHC
TNF receptor
Activated macrophage
TDTH secretions:
Cytokines: IFN-γ, TNF-β, IL-2, IL-3, GM-CSF
Chemokines: IL-8, MCAF, MIF
Effects of macrophage activation:
↑ Class II MHC molecules
↑ TNF receptors
↑ Oxygen radicals
↑ Nitric oxide


Hapten
Skin (sensitization site)
Langerhans cells
Stratum corneum
Epidermis
Dermis
Hapten
Skin (challenge site)
Regulatory CD4+ T cells
Efferent lymph
Afferent lymph
Draining lymph node
Effector CD8+T cells

Clinical applications:

1 - Allergic contact dermatitis (can occur due to wearing cheap jewelry (high amount of nickel salt) also due to some substances found in hair dyes)

2- TB granuloma (persistent antigen)

Diagnoses:

1- Delayed skin test (Mantoux test)

2- Patch test (for contact dermatitis)

3- Lymphocyte transformation test

Hypersensitivity special (yet not enough)

Type I	Type II	Type III	Type IV
- Atopic individuals - Non allergic people produce IgG - Also termed (Immediate Hypersensitivity, Anaphylactic reactions, Allergic reactions) -Antibody type: IgE -Cellular components (Mast cells, basophiles & eosinophil).	-Antibody: IgG or IgM. - Antigens: bound to cell membranes. -Exogenous antigens. -Examples: Glomerulonephritis and mismatched blood transfusion. -Diagnosed by Immunofluorescence.	-When antigen reacts with antibody the product is immune complex. Immune complex is capable of inducing an inflammatory response. - Immune complexes are deposited in tissues like kidneys (nephritis), joints (arthritis) or blood vessels (vasculitis). - Antibody (IgG or IgM) + Antigen (soluble) -Immune complex formation.	- Delayed hypersensitivity. -Cell mediated immune response -Antigen dependent T cell (CD4 generally and CD8 occasionally) activation via MHC Class I or II -Activated macrophages -Delayed onset (2-4 days) -Abnormal cellular response

-Antigens: low molecular weight & highly soluble. -Two phases: sensitization and challenge.	-Complement activation. -Attraction of inflammatory cells -Complex mediated inflammation reaction -Glomerulonephritis (Blood vessel wall) -Rheumatoid Arthritis, SLE -Diagnosis by Immunofluorescence.	(Granuloma formation) -Mediators released by T_{DTH} cells: chemokine, cytokines, chemo toxins. -Development of DTH Response: *Sensitization phase*: 1-2 week period *Effector phase:* 24-72 hours -Effector cells (Activated macs) Act non-specifically -Examples: Allergic contact dermatitis, TB granuloma (Persistent antigen) **-Diagnosis: Delayed skin test, Patch test Lymphocyte transformation test**

Brought to you by:

Ibrahim Al-qasir

Hossam Al- Shehri

Moath Al-Subaih

Bayan Al-Amr

Maha Al-Luhaidan