جامعة الملك سعود
King Saud University

Hypersensitivity Reactions

Color code:
Important in red
Extra in blue

Immunology
MED438

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For team error adjustments, click here

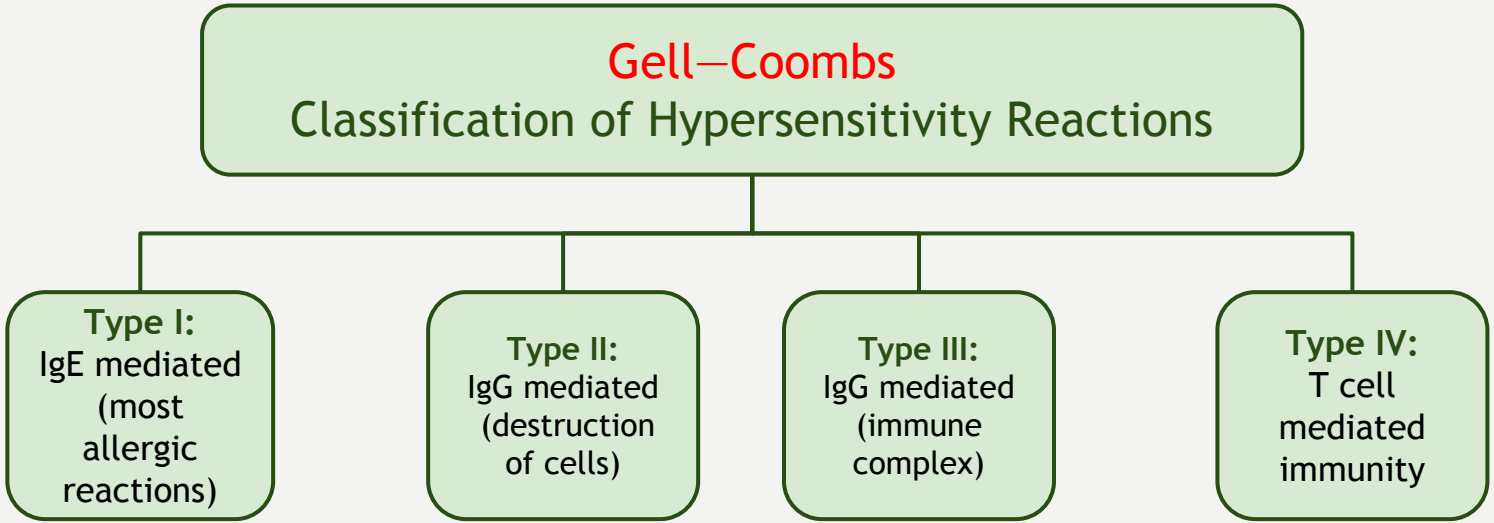
Objectives

- 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 mediate allergic inflammation
- To recognize that Type II hypersensitivity deals with immune responses against antigens that are integral parts of the 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

What is hypersensitivity?

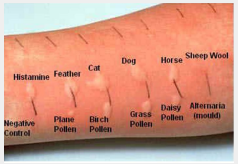
Hypersensitivity: is an undesirable reaction by the immune system.

Protective immunity: desirable reaction.



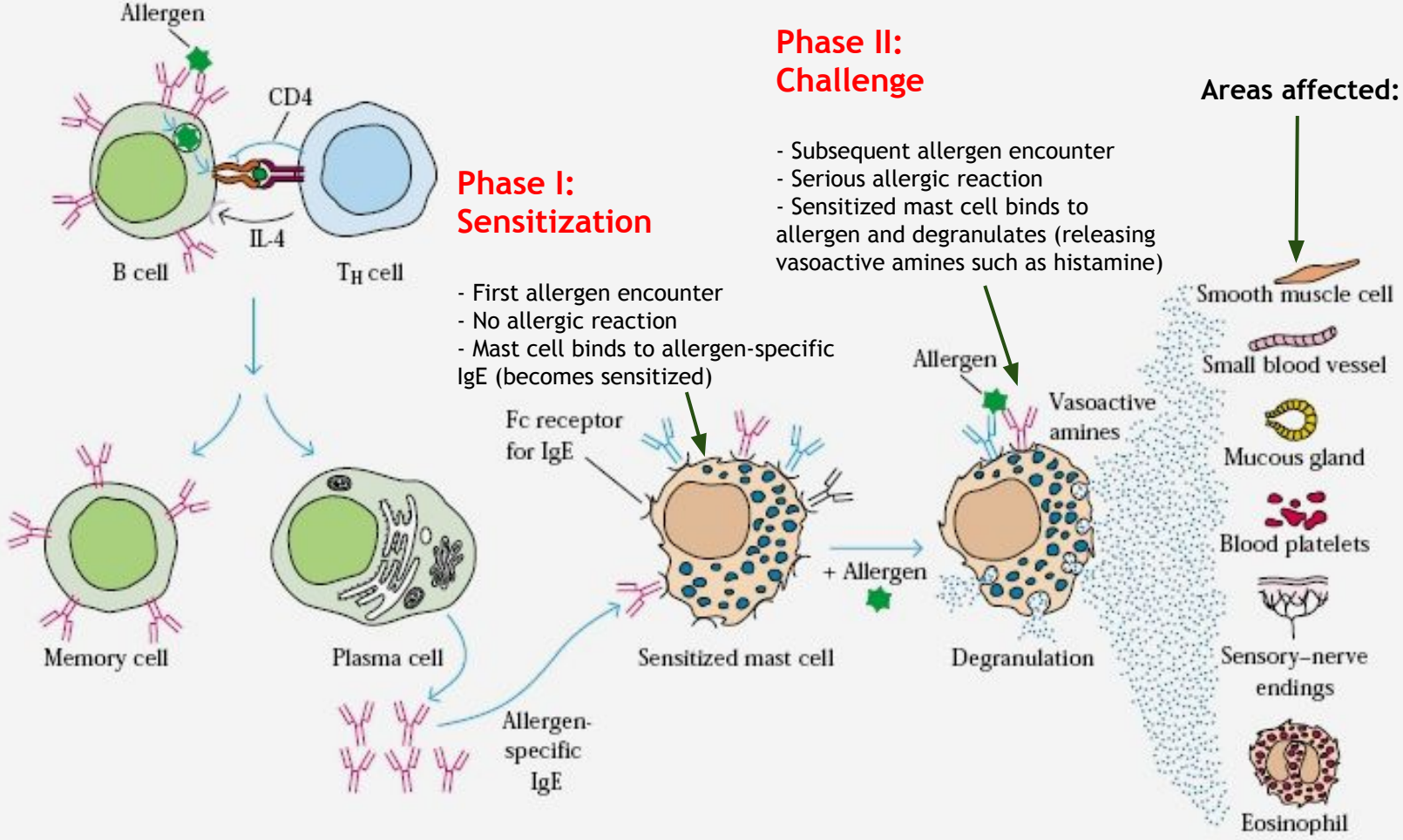
Type I Hypersensitivity

- Known as immediate hypersensitivity (mins-hrs) or an allergic reaction that may develop into an anaphylactic* reaction (a severe and life-threatening form).

Features	Antibody	- Allergic (atopic): IgE - Non Allergic: IgG
	Cells Involved	- Mast cells - Eosinophils - Basophils
	Antigen	- Allergen (low molecular weight & high solubility) Ex: Pollens, Dust mites, Injected allergen (sting venom from hymenoptera) Hymenoptera include bees, wasps, ants. They can cause systemic inflammation and anaphylactic shock
Clinical Examples	Allergy is a systemic disorder (affects multiple organs) - Food allergy (GIT) - Allergic Rhinitis and Asthma (Resp Tract) - Eczema, Urticaria, and allergic dermatitis (Skin)	
Diagonses	- Skin prick test (SPT) - Specific IgE measurement (RAST) - Elimination/Provocation test (Food allergy)	 SPT

*Unlike anaphylactic reactions, anaphylactoid reactions are non-IgE mediated and may result from local anesthetics or contrast media (show similar symptoms as anaphylactic)

Reaction Phases of Immediate Hypersensitivity



Allergic Mediators

No need to memorize everything (just know the basics) and how to differentiate between them.

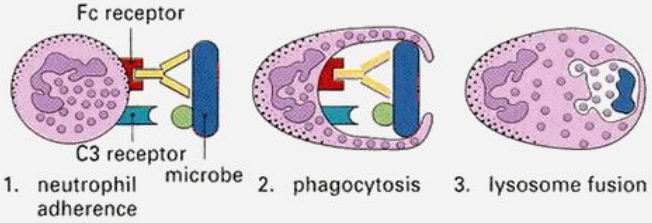
Mediators	Effects
Primary: are the main mediators released in an allergic reaction	
Histamine, heparin	Increased vascular permeability; smooth-muscle contraction
Serotonin	Increased vascular permeability; smooth-muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A)	Neutrophil chemotaxis
Proteases	Bronchial mucus secretion; degradation of blood-vessel basement membrane; generation of complement split products
Secondary: are the mediators released in response to the release of primary mediators	
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

Type II Hypersensitivity

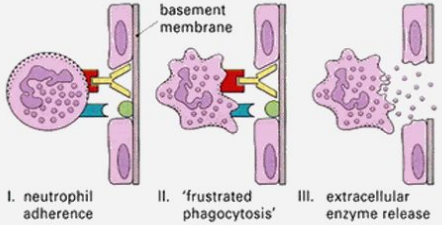
- Differs from type I in that the antigen is membrane-bound (not free), and it is highly related to autoimmune diseases.

Features	Antibody	- Mainly IgG, could be IgM (both can activate the complement system)
	Complement Activation	- Invariable (constant)
	Antigen	- Self Antigens (bound to cell membranes) - Exogenous antigens (microbial, also bounded)
Clinical Examples	- Glomerulonephritis (anti-glomerular basement membrane) - Mismatched blood transfusions	(diseases that injure the part of the kidney that filters blood called glomeruli)
Diagonses	- Antibody-antigen detection using Immunofluorescence	

Normal
Phagocytic function:



Type II
Phagocytic function:



Type III Hypersensitivity

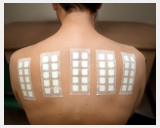
- Known as Immuno-complex Hypersensitivity. Happens when an antigen reacts with an antibody, forming an immune complex capable of inducing an inflammatory response.
- Immuno-complexes are deposited in tissues like:
  - Kidneys (nephritis) -Joints (arthritis) -Blood Vessels (vasculitis)

Features	Antibody	- Mainly IgG, could be IgM
	Complement Activation	- It is activated after the immuno-complex formation
	Antigen	- Free soluble antigen, unlike type II (bounded)
Clinical Examples	- Glomerulonephritis (Not basement membrane-bound) - Rheumatoid Arthritis - Systemic Lupus Erythematosus (SLE)	
Diagonses	- Immuno-complexes detection in blood/tissue using Immunofluorescence	

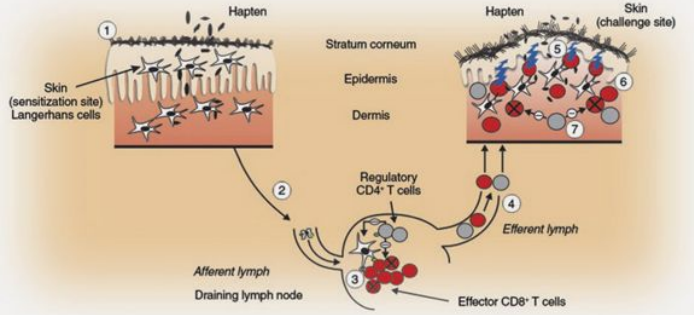
Vasculitis pathophysiology: Normally, macrophages will clear out large immuno-complexes after an immune reaction. However, sometimes there are small immuno-complexes that are hard for the macrophages to recognize, so they end up circulating in the blood and depositing in the vessels, leading to vasculitis

Type IV Hypersensitivity

- Known as delayed hypersensitivity-T_{DTH} (2-4 days) and cell-mediated hypersensitivity

Features	Antibody	- No antibodies (cell-mediated)
	Cells Involved	- Generally CD4 and occasionally CD8 - CD4 activates macrophages via Th1
	Antigen	- Presented to T cells by APCs (involving both MHC Classes)
Clinical Examples	- Contact Dermatitis (NOT to be mixed with Type I allergic dermatitis) - Granuloma formation (such as TB-persistent antigen) - Hair dyes	
Diagonses	- Delayed skin test (Mantoux test/Tuberculin test) - Patch test (used for contact dermatitis) →  - Lymphocyte transformation test	

Contact Dermatitis Pathophysiology

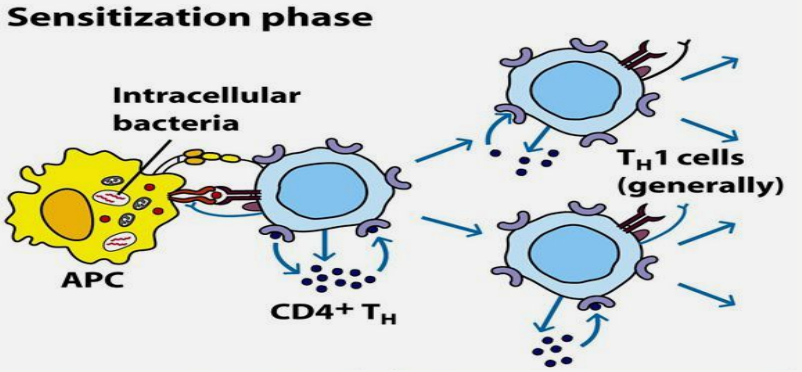


Hapten (eg. Nickel) : Small molecules that can't activate immune system without binding to larger proteins.

After binding, dendritic (langerhans) cells take the hapten to the lymph node where T cells recognize them and respond by heading to the infiltration site.

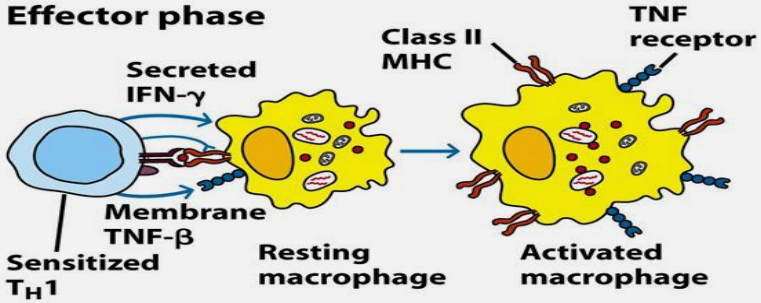
Reaction Phases of Delayed Hypersensitivity

Phase I (1-2 weeks)



CD4+ Th1 (generally) or CD8+ (occasionally) are activated by APCs via MHC Class I or II and become TDTH (delayed type T cell).

Phase II (24-72 hrs)



Sensitized TDTH secretes chemical mediators to activate macrophages that act non-specifically

Chemical mediators are:

- **Chemokines**: recruit macrophages (chemotaxis).
- **IFN-γ**: activates macrophages .
- **TNF α & β**: tissue destruction & increased adhesion.
- **IL-3/GM-CSF**: stimulate monocyte production.

Macrophage activation increases the following:

- MHC Class II -TNF receptors -ROS -Nitric Oxide

This causes tissue destruction

Take Home Message

- Type I (IgE), II (IgG) and III (IgG) hypersensitivity reactions are mediated by antibodies whereas Type IV hypersensitivity reaction is a cell mediated immune response.

- Hypersensitivity reactions are undesirable, excessive, and aberrant immune responses associated with disorders such as allergy, autoimmunity and chronic inflammation.

Quiz:

1. Antibody type in Hypersensitivity I:

a) IgG
b) IgD
c) IgE
d) Both A & C

2. Which of the following is a cellular component of Hypersensitivity I:

a) Macrophages
b) Neutrophils
c) Eosinophils
d) Lymphocytes

3. Antibody type in Hypersensitivity II:

a) IgE
b) IgG
c) IgD
d) Both B & C

4. The antigen of Type III Hypersensitivity:

a) Nuts
b) Free antigen
c) Dust mite
d) Bound to membrane

5. Which type of hypersensitivity produces immune complexes

a) Type I
b) Type II
c) Type III
d) Type IV

6. One of the following is NOT a chemical mediator in DTH

a) IL-3
b) IFNγ
c) TGF-β1
d) TNFα

1. D 2. C 3. B 4. B 5. C 6. C

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