University of Basrah, Medical College – Microbiology Department

Microbiology/ 3rd Year M.B.CH.B. Students

Part V: Basic & Clinical Immunology (17 hours)

Lecture 11

Duration: 1 hour

Hypersensitivity (Part I)

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Reference: Roitt's Essential Immunology 13th Edition

For more detailed instruction, any question, cases need help please post to the group of session.

Key definitions

Allograft: transplant of an organ or tissue from one individual to another of the same species with a different genotype (not identical twin).

Autograft: graft (tissue) from the same individual body.

Autoimmune hemolytic anemia: a rare red blood cell disorder (an immune disorder). IgG & IgM bind to Ags on transfused RBCs, targeting donor RBCs for destruction.

Idiopathic thrombocytopenic purpura (immune thrombocytopenia): an immune disorder in which the blood does not clot normally because the immune system destroys platelets leading to decreased number of platelets in the blood.

Goodpasture's syndrome (anti-glomerular basement membrane disease): rare autoimmune disease in which Abs attack the basement membrane in lungs & kidneys, leading to bleeding from the lungs &kidney failure.

Myasthenia gravis: an autoimmune disease of the neuromuscular junction caused by Abs that attack components of the postsynaptic membrane, impair neuromuscular transmission, & lead to weakness & fatigue of skeletal muscle.

Anaphylaxis: is a serious, life-threatening allergic reaction. The most common reactions are to food, insect stings, medications & latex. Immune system overreacts to allergen by releasing certain mediators.

Hemolytic disease of the newborn (HDN)(Erythroblastosis fetalis): IgG from mother crosses the placenta, targeting the fetus' RBCs for destruction.

Allergy March: Also called 'Atopic March' characterized by a typical sequence of IgE responses. In some children, eczema & allergies come in a specific order, as they get older. It starts with eczema, then food allergies, asthma, then hay fever.

Natural antibodies: immunoglobulins present in the absence of exogenous antigen stimulation.

Coombs test: direct coombs test can detects Abs bind to the surface of RBCs (used for autoimmune hemolytic anemia). Indirect Coombs test detects the presence of free Abs in the blood (used for prenatal testing of pregnant women & in testing prior blood transfusion.

Learning objectives (LO.s)

Hypersensitivity, how does it differ from normal immune response?	LO.1
Classification of hypersensitivity reactions	LO.2
Type I hypersensitivity: Immediate type (IgE-mediated mast cell degranulation)	LO.3
Type II hypersensitivity: Ab-mediated cytotoxicity	LO.4

Just to recap…

- Appropriate immune responses detect foreign Ags.
- Sufficient numbers of Ag-specific lymphocytes are generated by clonal proliferation
- Appropriate class of Ab is produce to clear the infection by binding to the surface of the pathogen.
- Formation of IgM- or IgG-containing immune complexes triggers the activation of classical complement pathway.
- IgG & complement components opsonize the pathogen for subsequent phagocytosis.
- IFN-γ (macrophage-activating factor), is produced by NK, Th1, & cytotoxic T-cells as a response to intracellular pathogens.

LO.1

Hypersensitivity, how does it differ from normal immune response?

Immune response that extends beyond its usual boundary of recognizing only foreign pathogens to also, encompass the innocuous environmental Ags leading to tissue damage (immunopathology).

The mechanisms underlying hypersensitivity reactions are the same as those normally employed by the body in combating infection. The problem is that they are:

1. Occurring with much too high an intensity

2. Directed against antigens that pose no threat

3. Taking place at locations in the body that are inappropriate.

LO.2

Classification of hypersensitivity reactions

Hypersensitivity originally classified by Gell & Coombs into (I-IV) and this classification remains broadly useful.

1. Type I: Immediate type (IgE-mediated mast cell degranulation)

2. Type II: Antibody-dependent cytotoxicity

3. Type III: Immune complex-mediated

4. Type IV: Delayed type (cell-mediated)

Some subsequent additions to the original classification have included:

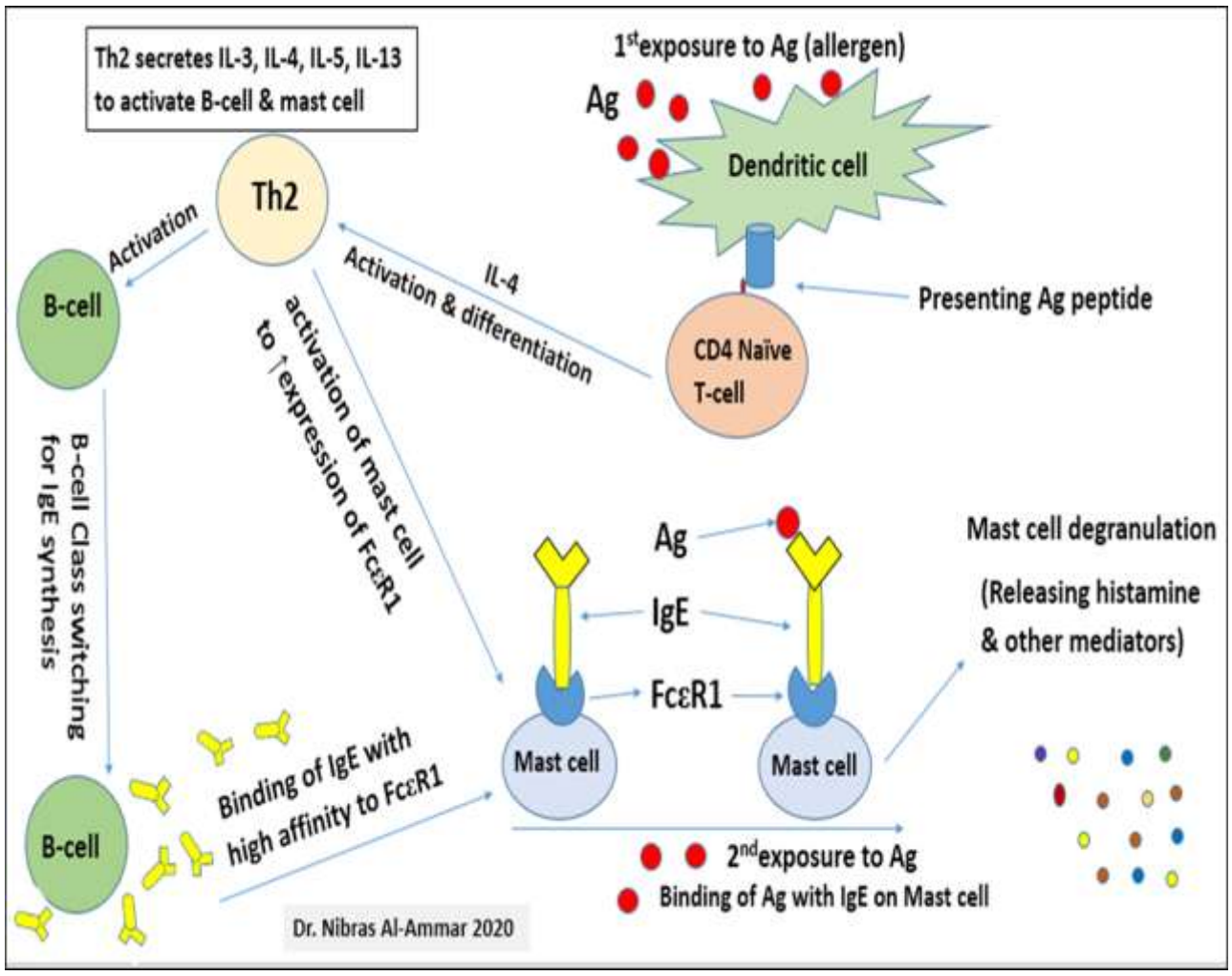
- **Type V: Stimulatory hypersensitivity**
- **Innate hypersensitivity**

Most allergies (hay fever & asthma, eczema, & food allergies) are mediated by type I hypersensitivity, although some forms of eczema are due to type IV reactions.

Note: in a particular disease more than one type of hypersensitivity may be operating.

LO.3

Type I: Immediate type (IgE-mediated mast cell degranulation)



LO.3

Preformed mediators that release after degranulation of mast cell

- **Histamine**
- **Heparin**
- **Tryptase**
- **Chymase**
- **Carboxypeptidase**
- **Eosinophil, neutrophil & monocyte chemotactic factors**
- **Platelet activating factor**
- **serotonin**

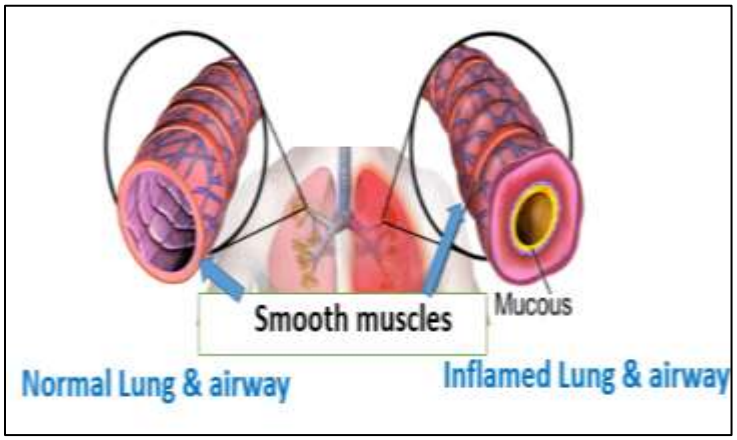
LO.3

Anaphylaxis

Results from mast cell degranulation and releasing its mediators

Characterized by:

- **Intense constriction of bronchioles & bronchi**
- **Constriction of smooth muscle**
- **Dilatation of capillaries**



LO.3

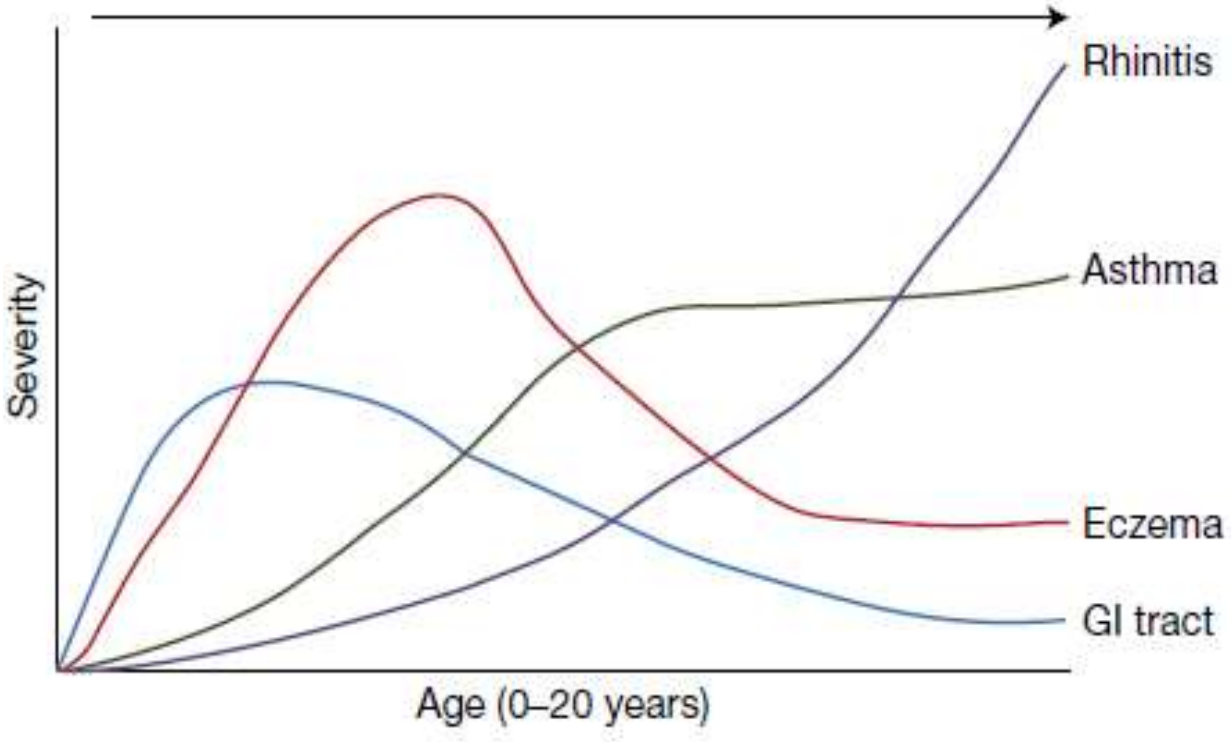
Atopic allergy

Clinically, type I hypersensitivity can manifests itself as immunological reactions in the:

- **Gastrointestinal tract**
- **Eczema (atopic dermatitis)**
- **Asthma & hay fever (seasonal conjunctivitis & rhinitis).**

These conditions often occur in the same individual; and develop in an ordered sequence called (allergy march).

Allergy march



Infants & children with gastrointestinal & cutaneous allergies have 2-3 fold increased risk of latter developing asthma & hay fever.

LO.3

Etiology of atopic allergy

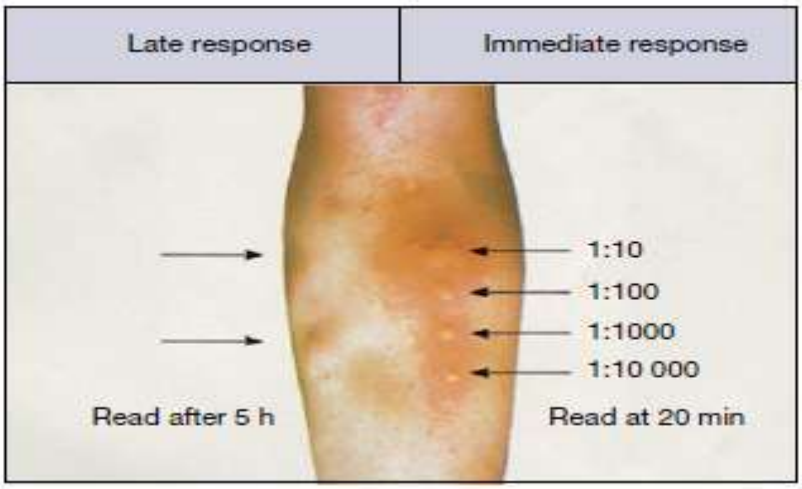
- Genetic factors (genes encoding HLA, cytokine etc.,)
- Various environmental factors
- Age
- Sex
- Infection history
- Nutritional status
- Allergen exposure
- The overall ability to synthesize IgE (the higher the level of IgE in the blood, the greater the likelihood of becoming atopic).

LO.3

Diagnosis

(Skin Prick test):

- Sensitivity normally assessed by the response to intradermal challenge with Ag.
- Release of histamine & other mediators rapidly produces an immediate *wheal & flare,* within 30 min and then subsiding.
- Followed by a late phase reaction in the injected skin (last for 24 h). (Dense infiltration with eosinophils & T-cells).



LO.3

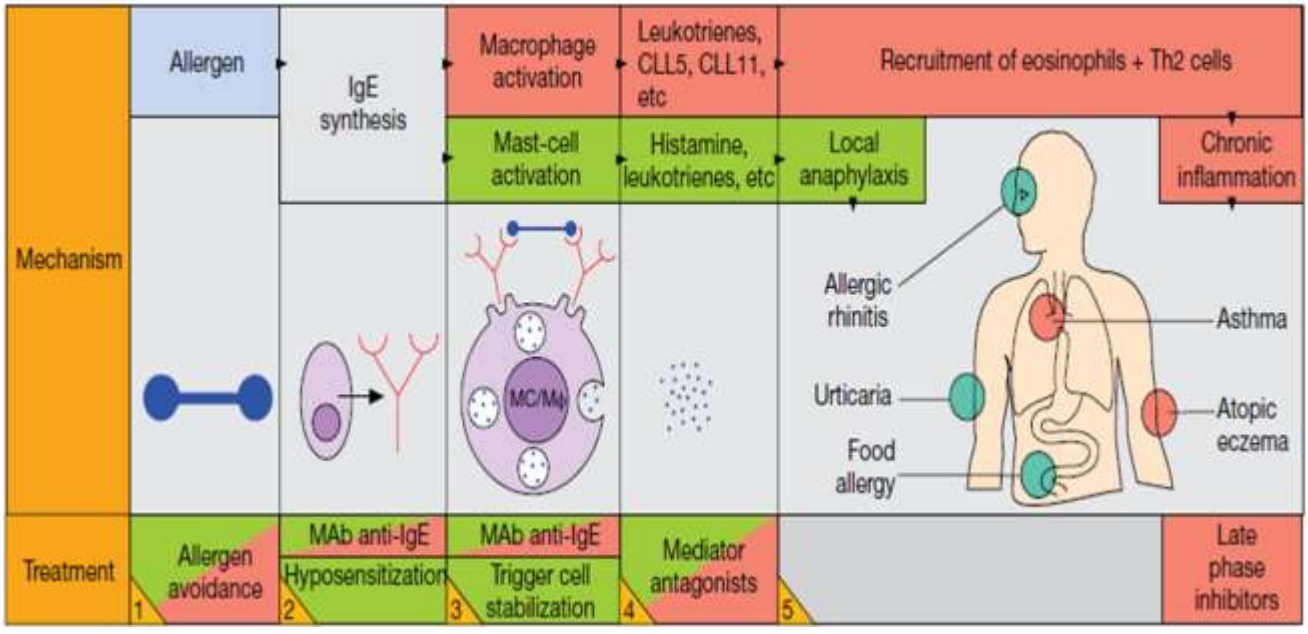
Measurement of allergen-specific serum IgE

- **Correlation between skin prick test responses & serum IgE is fairly good.**
- **In some instances, intranasal challenge with allergen may provoke a response even when both of these tests are (–ve), probably as a result of local synthesis of IgE Abs.**

LO.3

Several points in the chain of reactions provide targets for therapy:

- **Allergen avoidance**
- **Desensitization immunotherapy**
- **Blocking the action of IgE**
- **Inhibition of effector cells**
- **Mediator antagonism**
- **Limiting chronic inflammation**



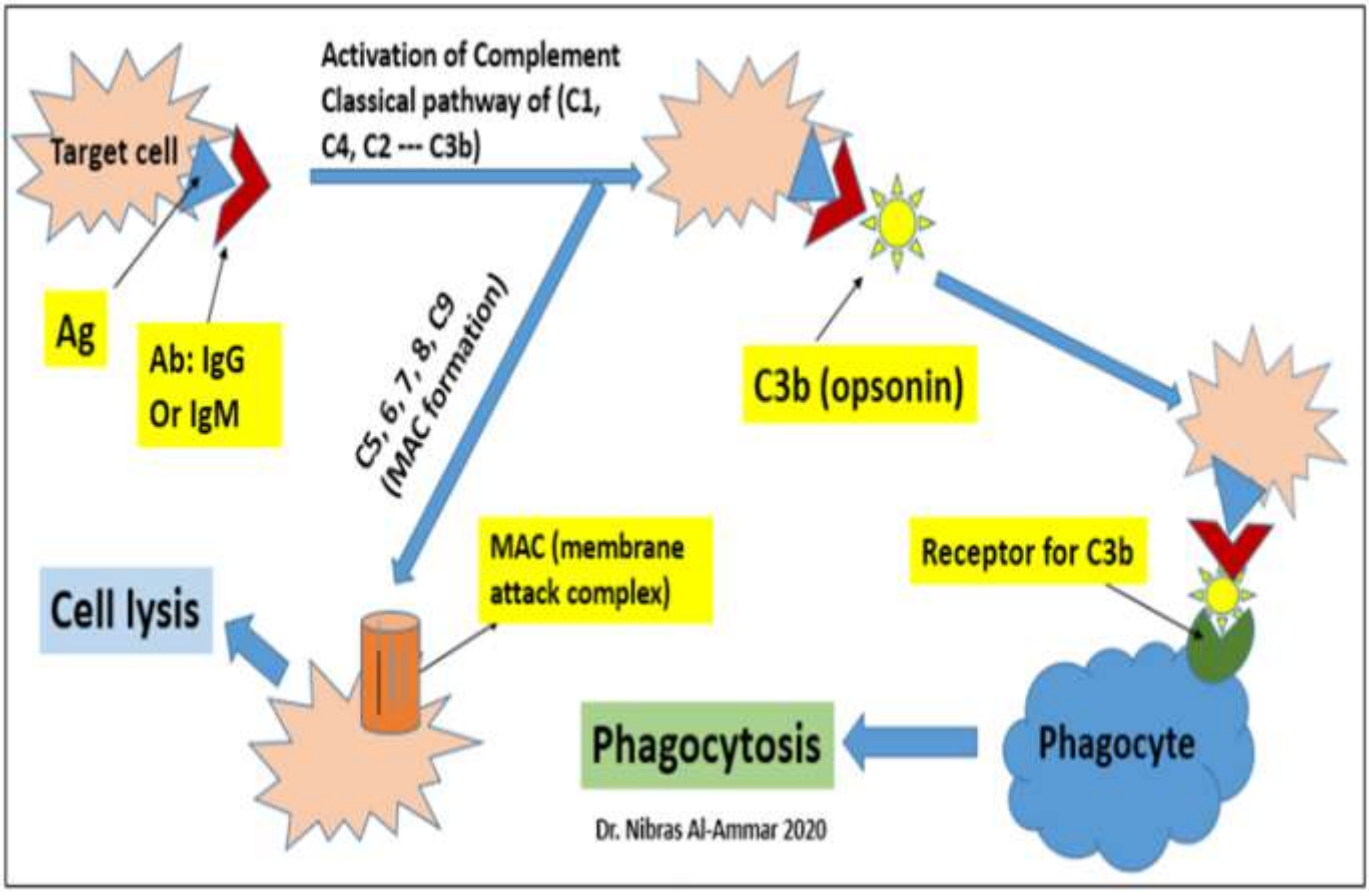
LO.4

Type II hypersensitivity-antibody-dependent cytotoxicity

Occurs through Two distinct cytotoxic mechanisms:

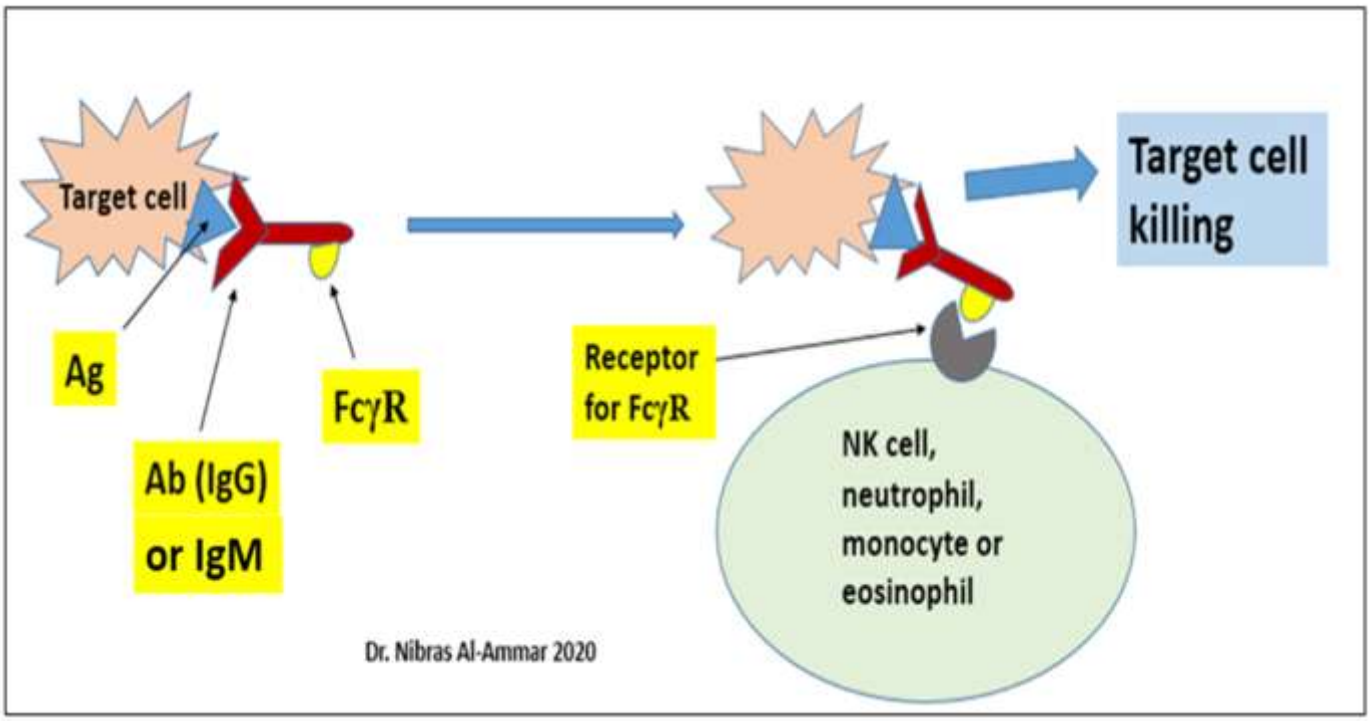
1. **Complement-dependent (cell- mediated cytotoxicity)(CDCC)**
2. **Ab-dependent cellular cytotoxicity (ADCC)**

1. Complement-dependent (cell- mediated cytotoxicity)(CDCC)



LO.4

2. Ab-dependent cellular cytotoxicity (ADCC)



LO.4

Type II reactions between members of the same species (Alloimmune reactions)

1. Abs to the A or B Ags of the *ABO blood groups:*

Occur spontaneously when Ag is absent from the RBC surface; thus; a person of:

Blood group A will have ----- anti-B

Blood group B will have ----- anti-A

Blood group O will have ----- both (anti-A & anti-B)

These antibodies (isohemagglutinins) are usually IgM and belong to the class of (natural Abs).

On transfusion, mismatched RBCs will be coated by the isoagglutinins, causing severe complement-mediated intravascular hemolysis.

LO.4

2. Maternal Abs (*Rh (rhesus) blood groups*

A mother with an RhD—ve blood group can readily be sensitized by RBCs from a baby carrying RhD Ags (RhD +ve) and forms (Anti-D Abs) This occurs at the 1st birth of the 1st child when a placental bleed can release a large number of baby's RBCs into the mother. Anti-D Abs are IgG (able to cross the placenta in any subsequent pregnancy). Diagnosis: by (Indirect Coombs test).

During subsequent pregnancy, Anti-D Abs will react with D Ags on the fetal RBCs leading to RBCs destruction through opsonic adherence, causing hemolytic disease of fetus & newborn (HDN) (Erythroblastosis fetalis).

LO.4

Other examples for Type II hypersensitivity diseases

- **Neonatal alloimmune thrombocytopenia**
    - **Solid organ allografts (in case of mismatched MHC)**
    - **Autoimmune type II hypersensitivity (Autoimmune hemolytic anemia)**
    - **Idiopathic thrombocytopenic purpura**
    - **Goodpasture's syndrome**
    - **Myasthenia gravis**

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Thank You