Course: Immunology
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Lecture: Hypersensitivity

Hypersensitivity

Allergy is inappropriate or disturbing immune response against certain antigens. Hypersensitivities are immunological reactions; they were classified for the first time by the scientists Gell and Coombs into four major types according to their immunological mechanisms:

1. Type I: Immediate Hypersensitivity.
2. Type II: Cytotoxic Hypersensitivity.
3. Type III: Immune complex Hypersensitivity.
4. Type IV: Delayed type Hypersensitivity.

Type I Hypersensitivity:

Usually called immediate , anaphylactic or atopic allergy. Has 3 arms or components; IgE/Mast cells/Allergen.

Allergen: is an antigen that stimulates Hypersensitivity, it is commonly innocuous environmental antigen (not harmful for normal peoples).

1. Causes or Motives:

1) Genetic susceptibility, this type of Hypersensitivity is usually hereditary.
2) Re-exposure to the same allergen.

2. Target:

Soluble Ag or allergen. Some of them are able to induce allergy directly after exposure e.g. house dusts and grass pollens. Other allergens need to combine with certain body proteins (act like haptens) e.g. pencillin antibiotic. While others may be changed inside human body and turn to allergic Ag like some foods after digestion.

3. Immunological Mechanisms:

First exposure or previous exposure:

1) Allergen (Ag) processed by APCs and certain Ags will be expressed on APCs surface.
2) B-cells response to APCs by producing specific IgE antibodies against that allergic Ag.
3) Binding of these IgE to the Fc reseptors of mast cells (or basophils).

Second exposure or re-exposure:

When the same Ag or allergen enters the body again; it will bind to the specific IgE on mast cells surface that stimulate the degranulation process to release the vasoactive and inflammatory mediators after series intracellular signal. The granules contain the mediators:

- ❖ Histamine
- ❖ Serotonin
- ❖ Lysosomal enzymes
- ❖ Heparin
- ❖ Eosinophils chemotactic factor ECF
- ❖ Prostaglandine
- ❖ Others

These mediators will be released to the neighboring tissues and fluids after degranulation. Then clinical signs appear depending on allergen type and allergic response either systemic or local. e.g. in asthma the symptoms or signs are: nausea, sneezing, hard to breath, asphyxia coughing, tearing eyes and others. **(Figure 1)**

Mast cells: they are basophils with more specification found in mucosa of airways and gut as well as in connective tissues. They have specialized surface receptors for the Fc portion of IgE antibodies.

4.Characteristics of this type of allergy:

Acute allergic reaction, starts immediately after exposure to allergen (within minutes) and lasts for 4-5 hrs.

Cause Eosinophilia (increase Eosinophils number in blood) and IgE levels increase.
Severity depends on the type of allergen, dose of exposure and immune system state. Most of these allergy kinds are seasonal e.g. Hey fever.

Examples:

- Hey fever
- Atopic dermatitis
- Asthma
- Pollen Allergy
- Food and drugs Allergy
- Vaccines Allergy

Clinical Example:

Anaphylaxis:

A systemic sever type I hypersensitivity, life threatening condition. Occurs when the allergy mediators are released in high amounts and mixed to form leukotrines mixture SRS-A (slow- reacting substance of anaphylaxis). This mixture is 1000 times powerful than histamine or prostaglandins in contracting bronchi.
This response physiological symptom starts with sudden anaphylactic shock, hard to breath, abdominal cramps (some time), diarrhea, vomiting and may end with death because of respiratory and cardiac failure.
Rapid administration of adrenaline (epinephrine) can stop shock progress. Epinephrine raises blood pressure and reverses the action of SRS-A (SRS-A drops down blood pressure), then restore respiratory and heart function. The important exampleis the systemic anaphylaxis that occurs after drugs like penicillin and bees biting. Blood pressure drops due to vasodilation after mediators' release. Also occurs in animals after injection with prepared Ags during immunization experiments.

Type II Hypersensitivity

It is usually called Antibody-Mediated or antibody-dependent cytotoxic hypersensitivity.

1. Causes or Motives:

Combination of surface Ag of the cell with specific Abs (IgG, IgM classes), resulting in the death of that cell by stimulating phagocytic attack or starting the complement pathway that leads to cell lysis. These cells are usually foreign cells e.g. RBCs during blood transfusion.

2. Target:

Antigens on cell surface (part of the cell membrane), not against soluble Ag.

3. Immunological Mechanisms:

When IgG or IgM antibodies bind to cell surface antigen forming Ag-Ab complex, this will cause cellular damage by many ways:

1) Activation of complement system (classical pathway).C3b deposition with anaphylatoxins C3a, C4a and C5a. then membrane attack complex formation which cause lysis of target cell.

2) Antibody-dependant cell-mediated cytotoxicity occurs when the Abs (Fab portion) bound to the surface Ag of the target cell. Then this bound Ab will also bind to the phagocytic cells and natural killer cells (NK) by Fc portion. Here the antibody works as a bridge between target cells and effector cells of the immune system. (**Figure 2)**

4. Characteristics of this type of allergy:

1) Clinical signs depend on the type of the cell that has the target antigen which induced this type of allergy. e.g. blood group hypersensitivity differ from graft rejection.
2) Need specific immune response and specific antibody.
3) Cause necrosis because of cells lysis.
4) Life threatening some times.

Examples:

- ☒ Blood grouping compatibility.
- ☒ Rh Incompatibility
- ☒ Graft rejection
- ☒ Newborn hemolytic disease

Clinical Example**:**

Hemolytic disease of newborn:

Rh incompatibility occurs when Rh- negative mother and Rh+ father. When the first fetus is Rh+ and during giving birth; the mother will expose to the Rh antigens of the fetus. During second child Rh+; the anti-Rh antibodies (IgG) that formed after the first child will cross the placenta and attack the Rh+ cells (RBCs) of the fetus. After birth the infant develops Jaundice or hemolytic disease of newborn. Before birth mothers liver filters the fetus blood. The treatment is by remove fetal Rh+ blood and replaced by Rh- blood to stop reaction between child Rh+ and antibodies of mother in child circulating blood that crossed placenta.

Mothers with Rh- negative avoid these cases by passive artificial immunization with Rhogam injections (anti-Rh antibodies commertialy called Anti-D). That to avoid memory immune response in mothers' blood.

Type III Hypersensitivity:

Called immune complex hypersensitivity. Results after some infections e.g. bacteria and during autoimmune diseases.

1.Causes or Motives:

1) High antigen load.
2) Weak or ineffective immune response.
3) Not enough function of macrophage to remove immune complexes from blood.

2.Target:

The antigen-antibody complex (Ag-Ab complex) which escape or avoid clear (engulfment) by macrophages and deposited in body tissues.

3. Immunological Mechanisms:

1) This type is also mediated by Abs(IgG or IgM) after forming, they bind to soluble Ag(resulting from bacterial infection for example).
2) Ag-Ab complex that formed will be cleared by MΦ.
3) Excess complex will deposit in any tissue and accumulate there.
4) Deposited complex will induce a number of inflammatory pathways or reactions to clear tissues like attraction of PMNLs, releasing of proteolytic enzymes causing local necrosis, vascular damage, odema, redness and attraction of more PMNLs because of activation of complement system which release of C3a, C4a and C5a anaphylatoxins, all these reactions end with tissues necrosis.

4. Characteristics of this type of allergy:

1) The painful inflammatory lesions will appear during this type of hypersensitivity in any tissue or organ that Ag-Ab complex deposited. That will lead to this organ disorder within 7-10 days after exposure to antigen.
2) Abs in this type formed during normal immune response against either exogenic Ag (infectious or environmental) or endogenic Ag (self Ag in autoimmune responses).

Examples:

- ✓ Rheumatoid Arthritis (Joints)
- ✓ Glomerulonephritis (Kidneys)
- ✓ Lymphodenitis (Lymph Nodes)
- ✓ Vasculitis (Blood Vessels)

Clinical Example**:**

Serum Sickness:

A disease occur because of type III hypersensitivity when a person get larg doses of foreign serum e.g. horse serum antitoxins to protect against Tetanus and Diphtheria.

Type IV Hypersensitivity:

Called Delayed type or cell-mediated type. Caused by a type of T-cells(CD4+) Lymphocytes which called T $_{DTH}$ (Delayed Type Hypersensitivity). This type is classified according to the clinical manifestations or signs and the body site that involved.

1.Causes or Motives:

Cell mediated immune response against certain Ags resulting from long standing infections or poisons exposure.

2.Target:

Ag coated cells of the body, the Ags are:

1) Natural products, mostly Haptens of low molecular weight, like poisons (ivy and oak) or industrial agents (Nickel compounds).
2) Prolonged infections (long standing) Ags like Leprosy, Tuberculosis, Brucellosis and fungal infections.

3.Immunological Mechanisms:

1) Need first exposure and second exposure to form memory T-cells.
2) Engulfment, processing and presenting allergic or foreign Ag.
3) Sensitization and activation of T $_{DTH}$ and the production of cytokines or lymphokines that involved in CMI e.g. Macrophage-activating factor MAF.
4) MΦ response and destroy Ag coated cells causing inflammation and necrosis.

4.Characteristics of this type of allergy:

1) It is called delayed because it occurs after 24-48 hr after exposure to allergic Ag.
2) Cell-mediated immune response involving MΦ, T-lymphocytes (T_{DTH}) and cytokines.
3) Cause Eosinophilia.

Examples:

- Contact Dermatitis (Eczema)
- Tuberculin reaction.

Clinical Example**s:**

☒ Contact Dermatitis:

When allergic compounds penetrate to skin (Hapten), they will bind to self protein and become immunogenic Ag , then expressed on APCs surface (langerhance). During second exposure to same Ag it will induce type 4 hypersensitivity causing itching, redness, rash and swallow of skin site of exposure.

☒ Tuberculosis:

Mycobacterium tuberculosis infection is long standing intracellular infection. When the Ag persist for long time, Granuloma will be formed. It's the most sever type of type 4 hypersensitivity. It is a type of chronic inflammation that involves tissues transformation or damage. Leprosy infections are the same.

Granuloma:

It is a cyst include phagocytic cells which turned to Giant cells(large multinucleus MΦ) , and intracellular pathogen with some epithelial cells. This can occur in lungs, heart and kidneys and cause tissues damage because of high amounts of lysosomal enzymes released to surrounding tissues.