**Hypersensitivity**

**Introduction**

Immune system provides protective as well as harmful response. Injury to immune system results in hypersensitivity and disease is called hypersensitive disease. The person who is sensitive to antigen that stimulate the immune response is sensitized person but excessive or pathological response of immune system in that person result in the hypersensitivity.

**Types of hypersensitivity**

There are 4 types of hypersensitivity:

1. Type I or Immediate hypersensitivity
2. Type II or antibody mediated hypersensitivity
3. Type III or antigen-antibody complex mediated hypersensitivity
4. Type IV or cell mediated hypersensitivity

**Type I hypersensitivity**:

Type I hypersensitivity is also called immediate hypersensitivity. This is the response of tissue that rapidly occurs after binding of antigen with IgE antibodies on surface of mast cells in sensitized persons. It occurs in a few minutes. This is also called allergic reaction.

Most important cells in that case are mast cells. Mast cells are usually located under blood vessels and sub-epithelial cells. In allergic patients, any allergen entered in their bodies, the allergen inhaled into the lungs where macrophages are present that destroyed the foreign particles and sometimes present allergen on their surface with the help of major histocompatibility molecule (MHC-II) that stimulate the TH2 cells of T-lymphocytes that release IL4, IL5 and IL13. These cytokines stimulate the β-cells as a result β-cells are proliferated and differentiated into plasma and memory cells.

The plasma cells secrete IgG and IgM antibodies against that allergen. In sensitive individual there is mutation in β-cells. In that individual IL4 and IL5 cause hyper activation of β-cells and result in the class switching of antibodies from IgG and IgM to IgE. These IgE antibodies circulate in our body and bind to the Fc receptors on mast cells. Again exposure to that allergen, the allergen binds with IgE antibody on the mast cells that cause degranulation of mast cells and produce immediate response that cause allergic reaction.

**Phases of allergy**

Allergic reaction usually occurs in two phases:

1. Early phase reaction
2. Late phase reaction

**Early phase reaction:**

In this, there is release of granular contents of mast cells e.g.

* Histamine
* Proteases
* Chemokine

Cyclooxygenase pathway is activated. As well as there is activation of phospholipase A enzymes that convert phospholipids into arachidonic acid and release prostaglandins. These mediators cause vasodilation, increased vascular permeability and smooth muscle spasm.

**Late phase reaction:**

In late phase reaction, arachidonic acid is converted to leukotrienes and platelet activating factors. Similarly in late phase reactions some cytokines are release from nucleus of mast cells that causes infiltration of neutrophils and cause bronchospasm e.g. Asthma.

**Type II hypersensitivity:**

It is also known as antibody mediated hypersensitivity. This type of hypersensitivity is caused by antibodies directed on the surface. In this type, antibodies cause disease:

* By activating cells for phagocytosis
* By activating complement system
* By altering cellular functions

**Opsonization and phagocytosis:**

When circulating cells such as erythrocytes or platelets are coated with auto-antibodies, as a result these cells become target for phagocytosis because phagocytes have a receptor for opsonins. This phagocyte has receptor against antibody which cause coating and stimulate the phagocytosis.

**Example:**

Most common example is hemolytic anemia.

**Activating complement system:**

Antibody targeted the cell surface antigen or protein, activate the complement system specifically it induce classical pathway for activation of complement system that results in production of complement components like C3a and C5a. C3a and C5a participate in chemotaxis and cause infiltration of monocytes and macrophages that stimulate inflammation. These antibodies activate the complement system and cause tissue injury.

**Example:**

Most common example is Pemphigus vulgaris.

This is the non-collagenous protein in the basement membrane of the kidneys and lungs that stimulate antibody production that stimulate complement system.

**Alteration of cellular function:**

Antibodies cause alteration of cell functions without involvement of complement system.

**Example 1:**

In myasthenia gravis, antibodies bind with Ach receptors on motor end plate of skeletal muscle and inhibit the neurotransmission that result in muscle weakness.

**Example 2:**

In graves’ disease antibodies against thyroid-stimulating receptors bind with that receptor on thyroid epithelial cells and stimulate the release of thyroid hormones that result in hyperthyroidism.

**Example 3:**

Another example is agglutination or erythroblastosis feotalis.

**Type III hypersensitivity:**

It is also known as antigen-antibody complex mediated hypersensitivity. It is formed in circulation may deposit into tissue leading to complement activation and acute inflammation. Antigen may be intrinsic or extrinsic.

Extrinsic antigen: Extrinsic antigen may be proteins and microorganisms.

Intrinsic antigen: Intrinsic antigen may be nuclear protein.

In this type of hypersensitivity, antigen freely circulate into the blood and interact with antibody and produce a complex. Normally this complex is formed and removed by phagocytosis. But in case of persistent infection, this complex is produced in large amount and not easily removed by phagocytosis. This antigen-antibody complex is known as pathogenic antigen-antibody complex. This pathogenic immune complex mediates systemic toxicity. When they are formed in circulation they deposit in all tissues. But in some cases, it may be localized and deposited in some specific tissues. The pathogenicity of systemic immune complex are divided into three different phases:-

* Phase I : antigen-antibody complex
* Phase II : deposition of complex into tissues
* Phase III : initiation and inflammatory response

**Examples:**

Phase I: Example of phase I is serum sickness which is the prototype of systemic immune complex disease. It was first time described in human when large amount of foreign serum was injected for passive immunization.

Another example is the production of antibodies in person with snake bite or a person who is receiving rabbit or horse serum containing anti-diphtheria antibody.

This antigen-antibody complex I usually removed by phagocytosis. But in excessive amount and persistent infection this complex is not removed by phagocytosis. As a result this complex is deposited in body tissues. The most common tissue for deposition are kidney, joints and small blood vessels.

This complex in our tissue activate the complement system that relieve various inflammatory and pro inflammatory components I-e :

C3a, C5a and prostaglandins. All these cause infiltration of neutrophils.

**Example:**

The resultant effect of pathogenic immune complex in our kidney results in glomerular nephritis, arthritis and vasculitis.

**Type-IV hypersensitivity:**

It is also known as cell-mediated hypersensitivity. Several immunological disorders and pathological reactions to the environment and persistent microbes are caused by T-lymphocytes. This type of hypersensitivity is called cell-mediated hypersensitivity.

**Types of T-lymphocytes:**

There are two types of T-lymphocytes:

1. Helper T-cell
2. Cytotoxic T-cell

Helper T-cells: Helper T cells are CD4 cells cause cytokine mediated inflammation.

Cytotoxic T-cells: Cytotoxic T-cells or CD8 cells cause direct toxicity.

**Types of cell-mediated hypersensitivity:**

There are two types of cell-mediated hypersensitivity:-

**1). Contact dermatitis:**

It is caused by poisonous substances which are poisonous oak, poisonous ivy and poisonous metals.

**2). Pathogenic substances:**

They may be intracellular or extracellular pathological reactions.

**Cytotoxic T-cells:**

When we come in contact with any substance, these substances absorb through skin then skin cells present the substance on their surface with the help of MHC-1 molecule.

These particular substance initiate allergic reactions and they are considered as antigenic substance or heptine. MHC-1 molecule activate the T-cell receptor on surface of T-killer cells. T-killer cells release perforins and grane enzyme. These perforins create holes in the target cells and grane enzyme enter through this hole into target cell and induce apoptotic pathway for cell death. This is called the direct toxicity of cell by killer cells. This usually cause graft VS host disease.

Similarly, this type of toxicity also develop in type-I diabetes mellitus in which pancreatic β-cells of insulin are destroyed by cytotoxic T-cells.

**Helper T-cells:**

When any pathogenic substance present on the surface of MHC-II molecule then these macrophages secrete cytokines especially IL-12, that cause proliferation of T-lymphocytes.

TH-1 cells secrete interferon-γ that cause activation of macrophages. This results in the increase phagocytosis and killing of pathogenic substance by free radical. These increased killing mechanism also cause local damage to local tissues. Similarly TH2 cells also secrete cytokines such as IL-4, IL-5 and IL-13. These cytokines attract eosinophil and cause degranulation of eosinophil and toxic proteins release that cause tissue damage. This is the cytokine-mediated hypersensitivity.