**Hypersensitivity Reactions (cont.)**

**2.Antibody-Mediated Diseases (Type II Hypersensitivity)**

Are caused by **antibodies (Ab)** directed against target antigens on the surface of cells or other tissue components.

**The antigens are either:**

**Intrinsic antigen**: normal antigens in the cell or

**Extrinsic antigens:** (drug metabolites) that deposit in tissues.

**Antibodies can cause disease via the following mechanisms:**

1-opsonization and phagocytosis.

2-Inflammation

3- Antibody-mediated cellular dysfunction.

**1. Opsonization and phagocytosis:**Ab target circulating cells like RBC and platelet and coat their surfaces (opsonize them) with or without complement proteins.

**Complement-dependent reaction**

**A-Direct lysis**: It is effected by complements activation, formation of membrane attack complex (C5 –9) . This MAC then disrupts cell membrane integrity by drilling a Hole through cell membrane lipid bilayer causing osmotic lysis of the cells,

**B- Opsonization**: By C3b, fragment of the complement to the cell surface enhances Phagcytosis. Then phagocytes (neutrophils and macrophages attack these cells through their receptors for the antibodies, or through their receptors for complement proteins)

• removal of cells usually occur in the spleen(and splenectomy could be part of the treatment for those diseases) like auto-immune hemolytic anemia and Autoimmune thrombocytopenic purpura.

**Examples**: include red blood cells, leukocytes and platelets disorders:

Transfusion reaction, autoimmune haemolytic anemia, autoimmune Thrombocytopenia and certain drug reaction

**2- Inflammation**

Antibodies (Ab) bind to antigens in tissues leading to complement activation, recruitment of leukocytes and tissue injury, E.g. some forms of glomerulonephritis and vascular rejection of transplanted organs occur by this mechanism. •**3- Antibody-mediated cellular dysfunction.**

Antibodies can bind to cell surface receptors or essential molecules, and cause functional derangements either inhibition (e.g. myasthenia Gravis), or unregulated activation (e.g. Graves disease ). NO inflammation or prominent tissue destruction seen by this mechanism.

**Myasthenia gravis** a disease characterized by muscle weakness, antibodies target acetylcholine receptors in the motor end plates of skeletal muscles block neuromuscular transmission and therefore cause muscle weakness.

The converse (i.e., antibody-mediated stimulation of cell function) is the basis In **Graves disease** , In this disorder, antibodies against the thyroid-stimulating hormone receptor on thyroid epithelial cells stimulate the cells, resulting in hyperthyroidism.

**3**. **Immune Complex Diseases (Type III hypersensitivity) :**

Are caused by antibodies binding to antigens to form complexes that circulate and deposit in vascular beds and stimulate inflammation, typically as a consequence of complement activation.

Complexes form either in the circulation or when antibodies bind to previously (planted) antigens in tissues (in situ immune complex)

**Antigens could be either:**

**External** (microbial or drug molecules) or

**Endogenous (self-antigens**) leading to autoimmune reactions

There are 2 types of Type III hypersensitivity (immune complex mediated):

**Systemic (serum sickness)** and **local (Arthus reaction)**

**A. Systemic Immune Complex Disease**

* Complexes are formed in the circulation and are deposited in several organs.
* The pathogenesis of systemic immune complex disease can be divided into three phases:

1-formation of immune complexes: after introduction of the foreign antigen, immune response is triggered and after about 1 week antibodies form and released into the circulation

2-deposition of complexes: in various tissues. The deposition tend to be systemic but preferentially involve kidney leading to chronic glomerular diseases or in joints (arthritis) or small blood vessels (vasculitis)

3-acute inflammation: due to complement activation or direct leukocytes activation.,

This phase occur around 10 days after antigen introduction with fever, joint pain and proteinuria

The antibody classes that induce such lesions are complement-fixing antibodies (i.e., IgG and IgM)

* The principal morphologic( **histopathological) manifestation** of type III reaction is small vessel vasculitis with fibrinoid necrosis of vessels walls and neutrophils infiltration
* **Types of systemic immune complex**:
* Acute type: results from inoculation to a single large volume to exogenous antigen, the lesions tend to resolve (self-limited) as a result of as the antigen is eliminated and catabolism of the immune complexes.

1-Acute serum sickness: It was first described in human when foreign serum was administered for passive immunization (e.g. horse anti tetanus serum). Now it is uncommon and seen infrequently.

2-poststreptococcal glomerulonephritis

2-**chronic type (chronic serum sickness**): results from repeated or prolonged and recurrent exposure to an antigen e.g. systemic lupus erythematosus.

* **B. Local Immune Complex Disease:**  
  in this type, the complexes are formed and deposited in a specific site.
* Local immune complex disease is characterized by a localized tissue vasculitis and necrosis.
* A model of local immune complex diseases is the :
* **Arthus Reaction**:it is a localized area of tissue necrosis resulting from acute immune complex vasculitis.
* It occurs after injection of an antigen into the skin of a previously immunized individual ( antibodies to that antigen are already present in the circulation),

As the antigen diffuses into the vascular wall, it binds the preformed antibody, and large immune complexes are formed locally.

These complexes precipitate in the vessel walls and cause fibrinoid necrosis, and superimposed thrombosis worsens the ischemic injury.

-Histopathologic Lesions: Inflammation, necrotizing vasculitis (fibrinoid necrosis).

**4. Cell–Mediated (Type IV) Hypersensitivity :**

Definition: The cell-mediated type of hypersensitivity is initiated by specifically sensitized T lymphocytes( without antibodies) .

Types: It includes 2 types:

1- **CD4+ Cell-Mediated hypersensitivity reaction**: Cytokines produced by the T cells induce inflammation that may be chronic and destructive. The classic example is : delayed type hypersensitivity reactions(DTH)

2-**CD8+ T Cell-Mediated Cytotoxicity**: direct cell cytotoxicity type: mediated by CD8+T cell.

**Delayed type hypersensitivity(DTH) :** Classically seen in:

1-granulomatous inflammation .

2-Tuberculin reaction .

3-contact dermatitis .

4-drug reaction.

5-some autoimmune diseases.

**Granulomatous inflammation**:

Occurs when persistent or nondegradable antigens (e.g., foreign bodies) lead to chronic macrophage activation manifesting as large epithelioid cells; nodules of these activated cells are called granulomas.

**Granuloma (Latin):** “small corn”: A nodular arrangement of inflammatory cells

**Pathogenesis of granulomatous inflammation:**

The sequence of events in DTH begins with the first exposure of the individual to tubercle bacilli. CD4+ lymphocytes recognize peptide antigen of tubercle bacilli in association with class II MHC on the surface of dendritic cells (APC).

Once CD4+ T lymphocytes recognize the antigen, it become sensitized with formation of TH1 type lymphocytes that develop memory cells and remain in the circulation for years.

On subsequent exposure to the same antigen, memory cells respond to the presented antigen on APC and become activated and secrete cytokines mainly TNF, IL-2 and IFN-ɣ.

IL-2 causes proliferation of T cells that have accumulated at the site of delayed type reaction

INF-ɣ is a potent activator of macrophages, it attract macrophages at the site of reaction from blood monocytes. Activated macrophages become large, flat and eosinophilic (called epithelioid cells) , some of these epithelioid cells under the influence of INF-ɣ fuse and form multinucleated giant cells. Epithelioid cells become surrounded by a collar of lymphocytes and fibroblasts and called granuloma and the pattern is called granulomatous inflammation.

Epithelioid cells produce potent products (proteases and oxide radicals) that are able to kill or neutralize mycobacteria and prevent dissemination of bacilli.

Loss of CD4+ T cells due to e.g. HIV infection, the ability of individual to respond against intracellular pathogens like mycobacteria is markedly impaired so mycobacteria are engulfed by macrophages but are not killed or inactivated and granuloma do not form leading to dissemination of tubercle bacilli

**Tuberculin Reaction**:

This reaction is found in individuals already sensitized to tubercle bacilli by a previous infection ( a previous exposure of individual to tubercle bacilli with formation of sensitized CD4+ T lymphocytes and memory cells).

Tuberculin is a protein extract of tubercle bacilli and within 8-12 hours of subcutaneous injection of tuberculin, a local area of erythema develops reaching its peak of 1-2 cm within 24-48 hours and then subsides gradually.

In this reaction, memory cells recognize tuberculin on surface of antigen presenting cells and secrete cytokines like IL-2 and INF-ɣ and causes accumulation of lymphocytes and macrophages in the perivascular area with local increase in vascular permeability leading to tissue indurations and local edema.

**Tuberculin reaction is used to:**  screen population for individuals who have prior exposure to tuberculosis and therefore have circulating memory cells,

so immunosuppression or loss of CD4+ T lymphocyte e.g., due to HIV infection leads to negative tuberculin test even in the presence of severe infection.

Tuberculin reaction: redness and induration in the skin after 8-12 hours and peaks at 24-72 hours with accumulation of T-helper cells and macrophages in the affected tissues around blood vessels, local increase in vascular permeability leading to tissue indurations and local edema

**3-Contact dermatitis:**  is another example of DTH by contact with certain chemicals (Nickle, latex, fragrance, cosmetics and hair dyes). Modify self-proteins or HLA molecules, these modified proteins will stimulate T-helper response that regard them as foreign antigen…leading to inflammatory reaction.

**4-Drug reactions** also involve modification of self-proteins by reactive chemicals leading to new-antigens and T-helper response with skin rash.

**5-Systemic autoimmune disease** like rheumatoid arthritis and systemic sclerosis involve DTH against self-antigens

**T-cell mediated cytotoxicity**

In this variant of type IV reaction, sensitized CD8+T cells kill antigen-expressing target cells.

T-cells in this reaction recognize foreign peptides in complex with MHC class I.

These cells are main defensive mechanism against:

1-viral infection: CD8+ kill viral infected cells which leads to elimination of the infected cells but this could also be the source of significant morbidity like in viral hepatitis

2-tumor cells.

3- Transplant rejection.

**Two mechanisms** by which CTLs cause T cell damage are:

A-Preforin-Granzyme : dependent killing where perforin drill a hole into the cell membrane with resultant osmotic lysis and granzyme activates apoptosis of the target cells

B-FAS-FAS ligand: dependent killing which induce apoptosis of the target cells.

**Autoimmune diseases**

**Autoimmunity**: Immune reactions to self antigens

**Immunologic tolerance:** Normal persons are unresponsive (tolerant) to their own (self) antigens, and autoimmunity results from a failure of self-tolerance.

**- Self tolerance**: lack of immune responsiveness one’s own tissue antigens.

The mechanisms of self-tolerance can be broadly classified into two groups:

1-central tolerance

2- Peripheral tolerance

**Central Tolerance:**

**Def.:** it is the process by which T and B cells that recognize self-antigens are either killed (negative selection) or rendered harmless during their maturation in central lymphoid organs (i.e., in the thymus for T cells and in the bone marrow for B cells).

If immature T-lymphocytes engaged with a self-antigen in complex with MHC molecules … transform into **regulatory T-cell** or **apoptosis.**

If immature B-cell engaged with self-antigen in the bone marrow it will undergo either:

**Receptor editing** (some of the self-reactive lymphocytes switch to new antigen receptors that are not self-reactive) or If receptor editing does not occur, the self-reactive cells) undergo **apoptosis**.

Central tolerance is not perfect because not all self-antigens present in thymus or bone marrow and self-reactive lymphocytes escape into peripheral tissue

**Peripheral Tolerance**

Self-reactive cells that escape central regulatory mechanisms can be removed or inactivated in the periphery through one of the following pathways:

**1-Deletion by apoptosis**. T cells that recognize self-antigens may receive signals that promote their death

**2- Anergy**: This term refers to **functional inactivation** (rather than death) of lymphocytes induced by encounter with antigens under certain conditions.

Each T-cell need two signals to be activated:

first from the antigen bound to MHC molecules

second from co-stimulatory receptors (which are found in low levels in normal circumstances) such as CD 28 must bind to their ligand called called CD80 or CD86 ( also known as B7-1 and B7- 2) on APC and if the Ag is presented by cell that do not bear CD 28 ligand (i.e B7-1 or B7-2) a negative signal is delivered and the cell becomes anergic.

Anergy also affects mature B cells in peripheral tissues.

if B cells encounter self antigen in peripheral tissues, especially in the absence of specific helper T cells, the B cells become unable to respond to subsequent antigenic stimulation .

**3-suppression by regulatory T lymphocytes** ( T reg. these cells develop mainly in the thymus and help control and inactivate self-reactive T-cells).

**4-hidden (sequestered) self-antigens**, from the immune system, e.g antigens in the testis, eye, and brain are relatively shielded from immune system, after trauma or infection they may induce prolonged inflammation like post-traumatic orchitis

When normal tolerance of the self antigens by the immune system fails, autoimmune diseases result.

**General pathogenesis of autoimmune diseases**

A normal body does not react against its own tissues.

However, several mechanisms can compromise this self tolerance, causing endogenous tissue to act as a pathogen. These include:

1- No central immune tolerance .

2- Interruption of clonal Anergy of autoreactive T cells .

3-Immortalization of activated T cells

4- imbalance of suppressor- Helper T-cell function:

loss of suppressor T cell function or excessive helper T cell function result in B cell activation

5- Formation of cross-reactive antibodies with specificity against pathogenic and endogenous HLA (molecular mimicry and antigen mimicry).

6- Emergence of hidden (sequestered) antigens: Some antigen are anatomically segregated from the developing immune system. Special clonal deletion or anergy fails to occur, if they release into circulation from tissue destruction by trauma or infection, they induced an immune response

7- Modification of molecule: if self-antigen is modified as due to drugs or microorganisms, this recognized by T cells as a foreign antigen so cooperate with B cells leading to formation of autoantibodies as in autoimmune hemolytic anemia

**Mechanisms of Autoimmunity**:

It is believed that the breakdown of self-tolerance and development of autoimmunity result from a combination of :

inherited susceptibility genes, which influence lymphocyte tolerance, and environmental factors, such as infections or tissue injury, that alter the display of self-antigens.

1-genetic factors in autoimmunity:

1-Autoimmune diseases have a tendency to run in families.

2-Several autoimmune diseases are linked with the HLA locus, especially class II alleles (HLA-DR, -DQ) e.g.

- Rheumatoid arthritis and HLA –DRB 1

-Ankylosing spondylitis and HLA- B 27

3-many genetic polymorphisms in ( non - HLA Genes) are associated with different autoimmune diseases.

e.g. PTPN-22 gene and type I diabetes and rheumatoid arthritis.

Polymorphisms in the gene for NOD2 are associated

with Crohn disease

2**- Role of infections and tissue injury:**

Microbes may induce autoimmune reactions by several mechanisms:

1-Viruses and other microbes may share cross-reacting epitopes with self antigens, This phenomenon is called molecular mimicry.

. (some microbes may express antigens that have the same amino acid sequences as self antigens. Immune responses against the microbial antigens may result in the activation of selfreactive lymphocytes. This phenomenon is called molecular mimicry. E.g rheumatic heart disease, in which antibodies against streptococcal proteins cross-react with myocardial proteins and cause myocarditis

2-Microbial infections with resultant tissue necrosis and inflammation can expose self-antigens and activate APCs and lymphocytes in the tissues.

Autoimmune diseases are, more common in women than in men, perhaps due to hormones and other factors.

**General Features of Autoimmune Diseases**

Diseases caused by autoimmunity have some important general features.

1-Autoimmune diseases tend to be chronic, sometimes with relapses and remissions, and the damage is often progressive.

2-Autoimmune diseases are more common in women than in men. perhaps due to hormones and other factors.

3-the clinical and pathologic manifestations of an autoimmune disease are determined by the nature of the underlying immune response.

Some of these diseases are caused **by autoantibodies**,

Most chronic inflammatory diseases are caused by abnormal and **excessive T helper responses** e.g psoriasis, multiple sclerosis, and some types of inflammatory bowel disease.

**CD8+ CTLs** contribute to killing of cells, such as islet -cells in type 1 diabetes.

In some autoimmune diseases, such as rheumatoid arthritis, both antibodies and T cell mediated inflammation may be involved.

4- In many of the systemic diseases that are caused by immune complexes and autoantibodies, the lesions affect principally the **connective tissue** and **blood vessels** of the various organs involved.

Therefore, these diseases are often referred to as **“collagen vascular**” or **“connective tissue**” disorders, even though the immunologic reactions are not specifically directed against constituents of connective tissue or blood vessels.

**Types of autoimmune diseases**:

**1-organ-specific disease**: specific immune responses are directed against one particular organ or tissue type and result in localized tissue damage.

**2-systemic or generalized disease**: multisystem diseases characterized by lesions in many organs and associated with multiple autoAbs or T cell–mediated reactions against numerous self-antigens.

**Why does some autoimmune disease affecting single organ while other are systemic?**

\* They depend on the nature of Ag:

(1) If Ag restricted in its expression to single organ e.g., Grave’s disease the autoimmune disease will be limited to the cells of that organ only.

(2) If more organs express the same Ag, so more wide spread diseases occur.

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