بسم الله الرحمن الرحيم

"قالوا سبحانه لا علم لنا إلا ما علمتنا إنك أنت العالم الحكيم،" البقرة- 32
Clinical immunology
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Hypersensitivity

- **Hypersensitivity** refers to: undesirable (damaging, discomfort-producing and sometimes fatal) reactions produced by the normal immune system.
Hypersensitivity reactions are classified into four types based on the mechanisms involved and time taken for the reaction:

1. type I, type II, type III (immediate reactions)
2. type IV (delayed reactions)
Type I Hypersensitivity (anaphylaxis)

- Type I hypersensitivity is also known as immediate or anaphylactic hypersensitivity.

- **Allergens:**
  1) **Inhalants:** Pollen grains, Fungal allergens
  2) **Injectants:** drugs
  3) **Contact:** cloths, antiseptic spray
Manifestations:

- Skin (urticaria and eczema),
- Eyes (conjunctivitis),
- Nasopharynx (rhinorrhea, rhinitis),
- Bronchopulmonary tissues (asthma)
- Gastrointestinal tract (gastroenteritis).
The mechanism of reaction involves production of IgE, in response to certain antigens (allergens).

IgE has very high affinity for its receptor on mast cells and basophils.

A subsequent exposure to the same allergen cross links the cell-bound IgE and triggers the release of various active substances.
Allergen

IgE antibody

Mast cell

Histamine containing granules

Degranulation

Inflammatory mediators

Symptoms: rashes, wheezing, vomiting
Mediators of Immediate Hypersensitivity

Preformed mediators in granules:

- Histamine: bronchoconstriction, mucus secretion, vasodilatation, vascular permeability
- Tryptase: proteolysis
- ECF-A (tetrapeptides): attract eosinophil and neutrophils

Newly formed mediators:

- Leukotriene B4: basophil attractant
- Leukotriene C4, D4: same as histamine but 1000x more potent
- Prostaglandins D2: edema and pain
Diagnostic tests for immediate hypersensitivity

- Skin (prick and intradermal) tests.
- Measurement of Total IgE and specific IgE antibodies: measured by ELISA.
Treatment:

A- Avoidance of exposure.
B- Symptomatic treatment.
C- Immunotherapy
Symptomatic treatment

1- **Antihistamines** which block histamine receptors.

2- **Chromolyn sodium** inhibits mast cell degranulation, by inhibiting Ca++ influx.

3- Late onset allergic symptoms, particularly bronchoconstriction which is mediated by leukotrienes, are treated with **leukotriene receptor blockers** or inhibitors of the **cyclooxygenase**.

4- Symptomatic, although short term, relief from bronchoconstriction is provided by **bronchodilators (inhalants)**.
Type II hypersensitivity

- Also known as cytotoxic hypersensitivity and may affect a variety of organs and tissues.

- The antigens are normally endogenous, although exogenous chemicals (haptens) which can attach to cell membranes can also lead to type II hypersensitivity.
Type II Hypersensitivity

K cell

Antibody dependent cell cytotoxicity

FeγRIII

macrophage
Types:

**RBCs lysis:**
1- Incompatible blood transfusion.
2- Erythroblastosis faetalis:
3- Autoimmune hemolytic disease.

**B- WBCs lysis:**
1- Granulocytopenia.
2- S.L.E.

**C- Platelet destruction:**
Type III Hypersensitivity (immune complex hypersensitivity).

- It is mediated by soluble immune complexes. They are mostly of the IgG, although IgM may also be involved. The antigen may be exogenous (chronic bacterial, viral or parasitic infections), or endogenous (non-organ specific autoimmunity: e.g., (SLE)).
Mechanism

- The antigen is soluble and not attached to the organ involved.

- Soluble antigen-antibody complexes which penetrate the endothelium of blood vessel and deposited on the vascular basement membrane.

- This will stimulate the complement and chemotactic factors like C5a is released which attract neutrophils which infiltrate the area and release lysosomal enzymes leading to destruction of the basement membrane.
Types

1- Arthus reaction:
2- Serum sickness:
3- Hypersensitivity pneumonitis:
4- Posstreptococcal glomerulonephritis:
5- Autoimmune disease: RA, SLE
Type IV Hypersensitivity

- Type IV hypersensitivity is also known as cell mediated or delayed type hypersensitivity.

- The classical example of this hypersensitivity is tuberculin (Montoux) reaction which peaks 48 hours after the injection of antigen (PPD or old tuberculin). The lesion is characterized by induration and erythema.
<table>
<thead>
<tr>
<th>Type</th>
<th>Reaction time</th>
<th>Clinical appearance</th>
<th>Histology</th>
<th>Antigen and site</th>
</tr>
</thead>
<tbody>
<tr>
<td>contact</td>
<td>48-72 hr</td>
<td>eczema</td>
<td>lymphocytes, followed by macrophages; edema of epidermis</td>
<td>epidermal (organic chemicals, poison ivy, heavy metals)</td>
</tr>
<tr>
<td>tuberculin</td>
<td>48-72 hr</td>
<td>local induration</td>
<td>lymphocytes, monocytes, macrophages</td>
<td>intradermal (tuberculin, lepromin)</td>
</tr>
<tr>
<td>granuloma</td>
<td>21-28 days</td>
<td>hardening</td>
<td>macrophages, epitheloid and giant cells, fibrosis</td>
<td>persistent antigen or foreign body presence (tuberculosis, leprosy)</td>
</tr>
</tbody>
</table>
Mechanisms of damage in delayed hypersensitivity include T lymphocytes and monocytes and/or macrophages. Cytotoxic T cells cause direct damage whereas Th1 cells secrete cytokines which activate cytotoxic T cells and recruit and activate monocytes and macrophages, which cause the bulk of the damage. The delayed hypersensitivity lesions mainly contain monocytes and a few T cells.

- Major lymphokines involved in delayed hypersensitivity reaction include monocyte chemotactic factor, IL-2, interferon-gamma, TNF alpha/beta, etc.
Diagnostic tests in vivo include delayed cutaneous reaction (e.g. Montoux test) and patch test (for contact dermatitis). In vitro tests for delayed hypersensitivity include mitogenic response, lympho-cytotoxicity and IL-2 production.
<table>
<thead>
<tr>
<th>characteristic</th>
<th>type-I</th>
<th>type-II</th>
<th>type-III</th>
<th>type-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>antibody</strong></td>
<td>IgE</td>
<td>IgG, IgM</td>
<td>IgG, IgM</td>
<td>None</td>
</tr>
<tr>
<td><strong>antigen</strong></td>
<td>exogenous</td>
<td>cell surface</td>
<td>soluble</td>
<td>tissues &amp; organs</td>
</tr>
<tr>
<td><strong>response time</strong></td>
<td>15-30 min.</td>
<td>minutes-hours</td>
<td>3-8 h.</td>
<td>48-72 h.</td>
</tr>
<tr>
<td><strong>appearance</strong></td>
<td>weal &amp; flare</td>
<td>lysis and necrosis</td>
<td>erythema and edema, necrosis</td>
<td>erythema and induration</td>
</tr>
<tr>
<td><strong>histology</strong></td>
<td>basophils and eosinophil</td>
<td>antibody and complement</td>
<td>complement and neutrophils</td>
<td>monocytes, lymphocytes</td>
</tr>
<tr>
<td><strong>transferred</strong></td>
<td>antibody</td>
<td>antibody</td>
<td>antibody</td>
<td>T-cells</td>
</tr>
<tr>
<td><strong>examples</strong></td>
<td>allergic asthma, hay fever</td>
<td>erythroblastosis fetalis, Goodpasture's nephritis</td>
<td>SLE, farmer's lung disease</td>
<td>tuberculin test, poison ivy, granuloma</td>
</tr>
</tbody>
</table>
TOLERANCE

• Definition:

Tolerance refers to the specific immunological non-reactivity to an antigen resulting from a previous exposure to the same antigen. When an antigen induces tolerance, it is termed tolerogen.
<table>
<thead>
<tr>
<th></th>
<th>Immune response</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical form of Ag</td>
<td>Large, aggregated, complex</td>
<td>Soluble, smaller, less complex</td>
</tr>
<tr>
<td>Route of Ag</td>
<td>SC or IM</td>
<td>Oral or IV</td>
</tr>
<tr>
<td>Dose of Ag</td>
<td>Optimal dose</td>
<td>Very large (sometimes very small)</td>
</tr>
<tr>
<td>Age of responding animal</td>
<td>Older and immunologically mature</td>
<td>Newborn, immunologically immature</td>
</tr>
<tr>
<td>Differentiation state of cells</td>
<td>Fully differentiated; memory T and B</td>
<td>Relatively undifferenten: B, T cells</td>
</tr>
</tbody>
</table>
Immunologic features of tolerance

• It is an active antigen-dependent process in response to the antigen.

• Like immune response, tolerance is specific and like immunological memory, it can exist in T-cells, B cells or both.
• Maintenance of immunological tolerance requires persistence of antigen.
• Tolerance can be broken naturally (as in autoimmune diseases) or artificially (by x-irradiation, certain drug treatments and by exposure to cross reactive antigens).
• Tolerance may be induced to all epitopes or only some epitopes on an antigen.
• **1- Clonal deletion:** Auto-reactive T-cells are eliminated in the thymus following interaction with self-antigen during their differentiation (negative selection). Likewise, differentiating early B cells become tolerant when they encounter cell-associated or soluble self-antigen.
2- **Clonal anergy:** Auto-reactive T cells, when exposed to antigenic peptides which do not possess co-stimulatory molecules (B7-1 or B7-2), become anergic to the antigen. Also, B cells when exposed to large amounts of soluble antigen down regulate their surface IgM and become anergic.
One method of the "co-stimulation" needed to activate T cells. If the T cell fails to receive "signal two", it dies by apoptosis. (B7 comes in two forms: B7-1 [CD80] and B7-2 [CD86].)
3) **Clonal ignorance:**

- *T cells* reactive to self antigen not represented in the thymus will mature and migrate to the periphery, but they may never encounter it (sequestered). Such cells may die out for lack of stimulus.

- Auto-reactive *B cells* that escape deletion may not find the antigen or the specific helper T cells and hence die out.
4) **Receptor editing:**
B cells which encounter large amounts of soluble antigen bind to it with very low affinity, undergo DNA recombination and change their specificity
5- **Anti-idiotypic antibody**: produced during the process of tolerization. They prevent the receptor from combining with antigen so inhibit immune response to it.
6- **Suppressor cells**: Both low and high doses of antigen may induce suppressor T cells, which can specifically suppress immune responses of both B and T cells.
Termination of tolerance

1- Prolonged absence of exposure to the tolerogen,
2- treatments which severely damage the immune system (x-irradiation)
3- Immunization with cross reactive antigens.
**Autoimmunity**

**Definition**

- Autoimmunity can be defined as breakdown of mechanisms responsible for self tolerance and induction of an immune response against components of the self. Such an immune response may not always be harmful (e.g., anti-idiotype antibodies).
Autoimmune diseases are generally classified on the basis of the organ or tissue involved.

- **organ-specific category** in which the immune response is directed against antigen(s) associated with the target organ being damaged.

- **non-organ-specific category** in which the antibody is directed against an antigen not associated with the target organ.
Autoimmune Diseases

**Nervous System:**
- Multiple sclerosis
- Myasthenia gravis
- Autoimmune neuropathies such as Guillain-Barré

**Skin:**
- Psoriasis
- Vitiligo
- Dermatitis herpetiformis

**Endocrine Glands:**
- Type 1 or immune-mediated diabetes mellitus
- Grave's Disease
- Hashimoto's thyroiditis
- Autoimmune disease of the adrenal gland (Addison's)

**Multiple Organs Including the Musculoskeletal System:**
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Scleroderma
- Sjögren's syndrome

**Blood:**
- Autoimmune hemolytic anemia
- Pernicious anemia
- Autoimmune thrombocytopenia

**Gastrointestinal System:**
- Crohn's Disease & Ulcerative colitis
- Primary biliary cirrhosis
- Autoimmune hepatitis
Blocking autoantibodies cause Myasthenia Gravis

acetylcholine receptors

anti AChR

signal blocked

receptors internalised and degraded
Genetic predisposition for autoimmunity

- Association between certain HLA types and autoimmune diseases has been noted (HLA: B8, B27, DR2, DR3, DR4, DR5 etc.).
Etiology of autoimmunity disease

Various theories:
- Sequestered antigen.
- Escape of auto-reactive clones.
- Loss of suppressor cells.
- Cross reactive antigens.
Sequestered antigen:

- Lymphoid cells may not be exposed to some self antigens during their differentiation, because they may be late-developing antigens or may be confined to specialized organs (e.g., testes, brain, eye). A release of antigens from these organs resulting from traumatic injury or surgery can result in the stimulation of an immune response and initiation of an autoimmune disease.
Escape of auto-reactive clones:

• The negative selection in the thymus may not be fully functional to eliminate self reactive cells. Not all self antigens may be represented in the thymus or certain antigens may not be properly processed and presented.
Diagnosis

-Symptoms:
- Antibodies against self-Ag:
  - Immunofluorescence (tissue-associated Ag)
  - ELISA or RIA (soluble Ag)
  - Biological or Biochemical assay (Graves dis.)
Treatment

1- Anti-inflammatory–Immunosuppressive.
2- Anti-TNF, Oral Ag, Anti-il-12, Anti-CD4, Anti-TCR.
• **A- Congenital**

• **Specific immune system:**
  - Stem cell  
  - B cell  
  - T cell  
  - Atypical

• **Non specific immune system:**
  - Phagocytes  
  - Complement
B- Acquired:

• Primary:
  - Physiological
  - Idiopathic

• Secondary:
  - Humoral
  - Cellular
Specific:

- **Stem cell**: (SCID) affects both T and B cell types.

- **B cell**: 
  Appear 3-6 months after birth 
  repeated bacterial infections 
  E.g., Bruton's hypogammaglobulinaemia.

- **T cell**: 
  Congenital absence or anomalies of the thymus 
  Viral, fungal, or protozoal infections. 
  E.g., Dsgeorge syndrome.

- **Atypical**: 
Non specific:

- **Phagocytes defects:**

  **Quantitative defects:**
  
  Deficiency in the number of phagocytes
  
  e.g., Congenital granulocytopenia

  **Qualitative defects:**
  
  Deficiency in one of the 4 stages of phagocytosis

- **Complement defects**

  Defects in chemotaxis or opsonization
Acquired immunodeficiency

Primary:

Physiological hypogammaglobulinaemia
Occurs in infants below 3-5 months of age, when maternal antibodies disappear and their own antibodies have not formed.

Idiopathic hypogammaglobulinaemia
Affects IgG, IgM, IgA with no known cause.
Secondary:

**Humoral:**
- Agammaglobulinaemia with thymoma:
- Low IgG:
- Low IgA and IgM:

**Cellular:**
- Malnutrition,
- Infections (AIDS)
- Malignancies as Hodjkin's disease
- Immunosuppressive agents as irradiation
- Cytotoxic drugs and corticosteroids
Transplantation Immunology

Transplantation is the transfer of cells, tissues or organs from one part of the body to another or from one individual to another.
Types of Grafts:

1. **Autografts** such as skin transplanted from one location to cover burns on another.
2. **Isografts**: Grafts between members of the same species with identical genetic makeup (identical twins or inbred animals).
3. **Allografts** from members of the same species.
4. **Xenografts** from members of different species.
Transplantation genetics:

- The genes coding for histocompatibility antigens can be divided into 2 groups:
  - 1-MHC where incompatibility leads to rapid rejection
  - 2-Minor transplantation antigens: incompatibility leads to slow rejection
Types:
1- Hyperacute graft rejection

- Occurs immediately upon transplantation.
- It is due to preformed antibodies, either: 
  Natural antibodies to blood type antigens, 
  Anti-MHC antibodies formed in response to 
  blood transfusions or 
  previous transplants, 
  or developed during pregnancy to the baby's paternal MHC antigens.

- Antibodies react with antigens on vascular endothelial cells 
  and activate complement.
- Resulting damage blocks blood vessels and starves the organ
2- Acute rejection:

- Occurs in the first weeks following transplantation.
- Symptoms include fever, a skin rash, impaired organ function (such as decreased urine output from a transplanted kidney), and a mononuclear (T cell) infiltrate into the graft visible on biopsy.

- Due to direct alloreactivity: Grafts contain passenger leukocytes, APC bearing both MHC and co-stimulatory molecules. Passenger leukocytes travel to the draining lymph nodes and activate recipient T cells.

- Effectors are primarily CTL.
3. Chronic (long term) rejection

- Due uptake of graft antigens by recipient APC and presentation on self MHC. Peptides from both MHC and minor H are presented by recipient APC.
- Effectors are usually Th1 cells that activate macrophages.
- T cells infiltrate the graft and produce cytokines that upregulate CAM expression on vascular endothelium and attract macrophages. Macrophages secrete IL-1, TNF-α, and the chemokine MCP to cause chronic inflammation.
- Chronic rejection and organ failure are due to arteriosclerosis of graft vessels, chronic toxicity of anti-rejection drugs, and infection with CMV.
Scenario 2: CHRONIC REJECTION
Continuous release of CM in the presence of subthreshold alloreponse

Activation of anti-CM memory B cells

Propagation of B cell response

Activation of naïve anti-CM Th2 cells

MHC class II

TCR

Co-stimulation

Cytokine help

Enhancement of immunity:
- Affinity maturation, isotype switching IgG1 -> IgG2a
- Complement activation
- Ab-mediated damage
- Endothelium activation
- Cytokines and growth factors production enhancement

Indirect Alloresponse
**Graft-versus-host disease (GVHD)**

- In bone marrow transplantation, the hematopoietic system of the recipient is completely destroyed by irradiation or cytotoxic drugs. Such preparation is required to make room for the transplanted marrow and may also be used to kill cancer cells if the transplant is being used as cancer therapy.

- GVHD responses occur to both MHC and minor H antigens.

- Symptoms of GVHD include rashes, diarrhea, and pneumonitis.

- Donor marrow can be treated before transplantation with antibodies to markers on mature T cells (anti-CD3, anti-CD4, and CD8).
<table>
<thead>
<tr>
<th>Type of rejection</th>
<th>Time taken</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyper-acute</td>
<td>Minutes-hours</td>
<td>Preformed anti-donor antibodies and complement.</td>
</tr>
<tr>
<td>Acute</td>
<td>Days-weeks</td>
<td>Primary activation of T cells</td>
</tr>
<tr>
<td>Chronic</td>
<td>Months-years</td>
<td>Causes unclear: antibodies, immune complexes, slow cellular reactions, recurrence of disease.</td>
</tr>
</tbody>
</table>
PROCEDURES TO ENHANCE GRAFT SURVIVAL

1-Donor selection

- The most important in donor selection is the MHC identity with the recipient; an identical twin is the ideal.
- Grafts from an HLA-matched sibling have 95-100% chance of success.
- One haplotype-identical parent or sibling must match at the HLA D region.
- A two haplotype-distinct donor with a reasonable match for D-region antigen can also be used.
- Organs from a two or one DR matched cadaver have been used also with some success.
- In every case, an ABO compatibility is essential.
2-Recipient preparation

- The recipient must be infection-free and must not be hypertensive.

- One to five transfusions of 100-200 ml whole blood from the donor at 1-2 week intervals improves the graft survival and is practiced when possible.
3-Immunosuppression

A - Anti-inflammatory agents
Corticosteroids block inflammation. The most commonly used is prednisone.

B - Cytotoxic drugs
They block DNA synthesis and affect rapidly dividing cells.
- Azathioprine and cyclophosphamide are the most commonly used.
- Cyclosporin A and tacrolimus: cause non antigen-specific immunosuppression and are expensive and toxic to the kidneys and other organs.
# Immunosuppressive Effects of Cyclosporin A and Tacrolimus

<table>
<thead>
<tr>
<th>Cell</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>T cell</td>
<td>Reduced expression of IL-2, IL-3, IL-4, GM-CSF, TNFα</td>
</tr>
<tr>
<td></td>
<td>Reduced proliferation</td>
</tr>
<tr>
<td></td>
<td>Reduced Ca$^{2+}$-dependent exocytosis of granule-associated serum esterases</td>
</tr>
<tr>
<td></td>
<td>Inhibition of antigen-driven apoptosis</td>
</tr>
<tr>
<td>B cell</td>
<td>Reduced proliferation due to reduced IL-2</td>
</tr>
<tr>
<td></td>
<td>Inhibition of proliferation following antigen binding</td>
</tr>
<tr>
<td></td>
<td>Inhibition of apoptosis following B cell activation</td>
</tr>
<tr>
<td>Granulocyte</td>
<td>Reduced Ca$^{2+}$-dependent exocytosis of granule-associated serum esterases</td>
</tr>
</tbody>
</table>
c-Anti-Lymphocyte Globulin (ALG)

ALG is serum from a horse immunized with human lymphocytes; when injected into humans it kills lymphocytes.
TUMOR IMMUNOLOGY
• Cancer cells originate from a single transformed cell that undergoes unregulated cell proliferation.

• **Solid tumors** are collections of attached cancer cells which can metastasize (spread) from their original site.

• **Liquid" tumors** are leukocyte tumors that circulate in the blood and may also form masses elsewhere in the body.

- Cancer results from several sequential events, including:
  - genetic predisposition
  - transformation by viruses
  - environmental mutagens (radiation and chemicals).
Evidence for immune reactivity to tumors

- Tumors that have severe lympho-reticular infiltration have a better prognosis.
- Certain tumors regress spontaneously (e.g., melanomas).
- There is an increased incidence of primary and secondary malignancies in immunodeficient patients.
- Antibodies and immune T lymphocytes have been detected in patients with tumors.
- The young and the very old have an increased incidence of tumors.
- Animals can be specifically immunized against various types of tumors.
In order for the immune system to react against a tumor, the latter must have antigens that are recognized as foreign. A number of alterations occur in the cell during tumorigenesis (e.g., enzymes, receptors, membrane antigens, etc.).
Antigenic changes in malignant cells

1- Suppression of membrane proteins that are essential for immune recognition and activation

2- Surface membrane molecules which might be antigenically novel including:
   - reappearance of fetal antigens (onco-fetal antigens),
   - expression of unique antigens not expressed by normal cells.
   - Neo-antigens that contribute toward tumor rejection are referred to as tumor associated transplantation antigens (TATA).
1-Onco-fetal antigens

A- Alpha-fetoprotein
- A 5-fold or higher rise in this protein is used for monitoring hepatomas and testicular cancers.

B- Carcinoembryonic antigen
- Levels that are 4-5 times normal have been used to predict recurrence of colorectal tumors.
2. Tumor associated transplantation antigens (TATA):
   1. TATA on viral tumors

- Viruses are involved or suspected to be involved in some human malignancies such as:
  - HTLV-1 in leukemia,
  - hepatitis-B virus in hepatic carcinoma,
  - papilloma virus in cervical cancer.

- Virus-induced tumors express cell surface antigens (distinct from antigens of the virion itself) which are shared by all tumors induced by the same virus.
2. TATA on chemically-induced tumors

- These unique antigens on chemically-induced tumors are referred to as tumor specific transplantation antigens (TSTA) also called tumor rejection antigens (TRA).
Immunity against tumors

A- Natural immunity:
1- Natural Killer cells (NK):
   Population of large granular lymphocytes which can kill tumor cells.
2- Macrophages:

   B- Cell mediated immunity:
   T cell response and B cell response (antibodies capable of lysis of tumor cells)
• Tumors may not express neo-antigens that are immunogenic or they may fail to express co-stimulatory molecules for the activation of T-cells.

• Certain tumors are known to lack or be poor expressers of MHC antigen.
• In the early development of a tumor, the amount of antigen may be too small to stimulate the immune system and, due to the rapid proliferation of malignant cells, the immune system is quickly overwhelmed.

• Some tumors may evade the immune system by secreting immunosuppressive molecules and others may induce suppressor cells.

• Some tumors may shed their unique antigens which block antibodies and T cells from reacting with malignant cells.
Use of tumor neo-antigens in patient management

1-Immuno-diagnosis
- Monoclonal antibodies labeled with radioisotope have been used for in vivo detection of relatively small tumor foci.

2-Immunotherapy
- Immunotherapy has been used as adjuvant to traditional treatments.
- Both active and passive means of stimulating the non-specific and specific immune systems have been employed, in some cases with significant success
## Immunotherapy of tumors

<table>
<thead>
<tr>
<th>Type</th>
<th>Active</th>
<th>Non-Specific</th>
<th>Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG, Propionibacterium acnes</td>
<td><strong>active</strong></td>
<td><strong>non-specific</strong></td>
<td>killed tumor cells or their extract, recombinant antigens, idiotype, co-stimulatory molecule genes, etc.</td>
</tr>
<tr>
<td>LAK cells, cytokines</td>
<td><strong>passive</strong></td>
<td><strong>non-specific</strong></td>
<td>antibodies alone or coupled to drugs, pro-drug toxins or radioisotope; bispecific antibodies; T-cells</td>
</tr>
<tr>
<td>LAK cells and bispecific antibody</td>
<td><strong>combined</strong></td>
<td><strong>specific</strong></td>
<td></td>
</tr>
</tbody>
</table>
• A variety of immunopotentiating agents (biological response modifiers) are used to enhance anti-tumor immunity.

• They include bacterial products, synthetic chemicals and cytokines.

• Most of these agents exert their effects by activating macrophages and natural killer (NK) cells, eliciting cytokines or enhancing T-cell functions.

• Cytokines include IFN-alpha, beta, gamma, IL-2 and TNF-alpha
Macrophage

Chimeric monoclonal antibody

Monoclonal antibody-Toxin conjugate

Radiolabeled monoclonal antibody

NK cell

Enzyme locally converts prodrug to drug
• **Definition:**

Material-containing antigens derived from one or more pathogenic organisms which on administration to man or animal will stimulate active immunity and protect against infection by these or related organisms.
Vaccine Types:

1. Inactivated (killed) vaccine:

*Inactivation can be induced by heat, chemical or UV irradiation.*

- **Salk polio vaccine**: A mixture of three serotypes of polio virus is sufficient to generate good protective immunity against all common polio viruses.
- **Influenza virus vaccine**
- **T.A.B. vaccine**: heat killed vaccine (enteric fever)
- **Koll's vaccine**: heat killed vaccine against cholera
- **Haffkin's vaccine**: heat killed vaccine (plague)
- **Cox vaccine**: formalin killed vaccine (Rickettsial diseases)
II. Attenuated (weakened) vaccines:

- The pathogen is grown in animals or tissue culture under conditions that make it less virulent.
  - 1. The Sabin oral polio vaccine: The oral polio vaccine is being used in the WHO polio eradication campaign
  - 2. measles, mumps, and rubella
  - 3. BCG vaccine: The only example of live bacterial vaccine is one against tuberculosis (*Mycobacterium bovis*: BCG).
Advantages of virus attenuated vaccines

• Can stimulate cellular and humoral immune responses.
• Needs less virus to be injected (can multiply within the host).
• It stimulates response to antigens in their natural conformation.
• Can be administered orally which is less expensive than injections.
• Oral administration induces mucosal immunity and IgA synthesis, which gives more protection at the normal site of virus entry.

Disadvantages of attenuated vaccines

• The virus may very rarely revert to its virulent form.
• Cannot be given safely to immunosuppressed.
III. Subunit vaccines

- Contain purified antigens rather than whole organisms; *(Bordetella pertussis* antigens included in the acellular DPT vaccine).*

**Advantages**
- Not infectious, so they can be given safely to immunosuppressed people.
- They are less likely to induce unfavorable immune reactions.

**Disadvantages**
- The antigens may not retain their native conformation, so that antibodies produced against the subunit may not recognize the same protein on the pathogen surface.
- Isolated protein does not stimulate the immune system as well as a whole organism vaccine.
Adjuvants:

• The effectiveness of subunit vaccines is increased by giving them in Adjuvants to slow antigen release for a more sustained immune stimulation.

• Alum (aluminum salts) is a common adjuvant in the form of aggregates proteins to make them easier for phagocytes to engulf.

• Pertussis toxin, one of the components of theacellular DPT, acts as an adjuvant in that vaccine (see conjugate vaccines).

• Some bacterial components used as adjuvants in animals but which cause too much inflammation to be safe in humans are whole *Mycobacterium tuberculosis*, muramyl dipeptide from Mycobacterial cell walls, and bacterial DNA.
IV. Toxoid vaccines:

- The diphtheria and tetanus toxoid components of DPT are examples.
- These are toxins that have been treated to eliminate their toxicity; they are still able to induce antibodies that can neutralize the native toxins.
V. Conjugate vaccines

Have been developed to pathogens whose polysaccharide capsules protect them from phagocytosis:

*Haemophilus influenzae* B (HiB),
*Streptococcus pneumoniae*, and
*Neisseria meningitidis*.

Immunity to these organisms requires opsonizing antibodies, and T-independent responses to polysaccharide antigens. By linking the polysaccharides to protein carriers, they are converted into T-dependent antigens and protective immunity is induced.

HiB polysaccharide is complexed with diphtheria toxoid to increase its immunogenicity in infants.
VI. Peptide vaccines

- These vaccines target particular peptides to which a protective response can be developed.

- Peptides have no native structure and do not bind the recognition molecules on phagocytes that promote pathogen uptake.
The only recombinant vaccine currently in use in humans is the Hepatitis B Virus (HBV) vaccine, which is a recombinant subunit vaccine.

Hepatitis B surface antigen is produced from a gene transfected into yeast cells and purified for injection as a subunit vaccine.

This is much safer than using attenuated HBV, which could cause lethal hepatitis or liver cancer if it reverted to its virulent phenotype.
VIII. DNA vaccines

- Are the newest vaccines and seem to be very effective and safe.
- Like recombinant vaccines, genes for the desired antigens are located and cloned.
- In the case of DNA vaccines, the DNA is injected into the muscle of the animal being vaccinated, usually with a "gene gun" that uses compressed gas to blow the DNA into the muscle cells.
- Both humoral and cellular immunity have been induced by DNA vaccines.
THANK YOU