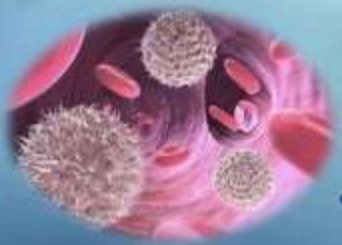
IMMUNOPHARMACOLOGY



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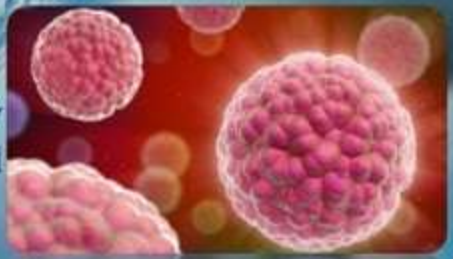
INTRODUCTION

- Immunopharmacology is the study of the effects of the drugs modifying immune mechanism in body.
- It includes not only inoculation but also autoimmune disorders, allergic reactions, and cancer.
- A significant development has new approach to control the immunological mechanism by drugs.

  Eg. Immunosuppressant.



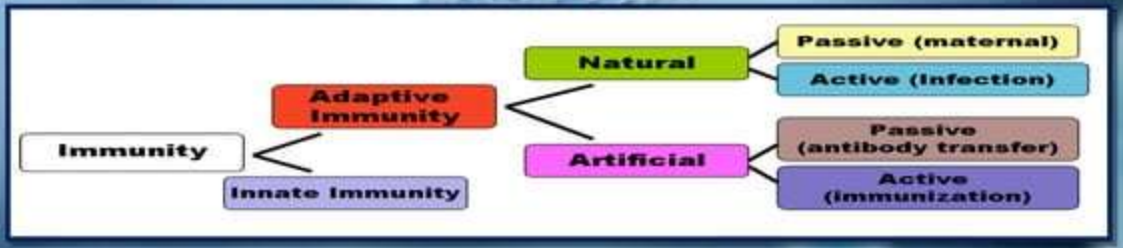
THE IMMUNE SYSTEM

IMMUNITY :

- It is the ability of the living body or the process to resist various types of organisms or toxins that tend to damage the tissue and organs.

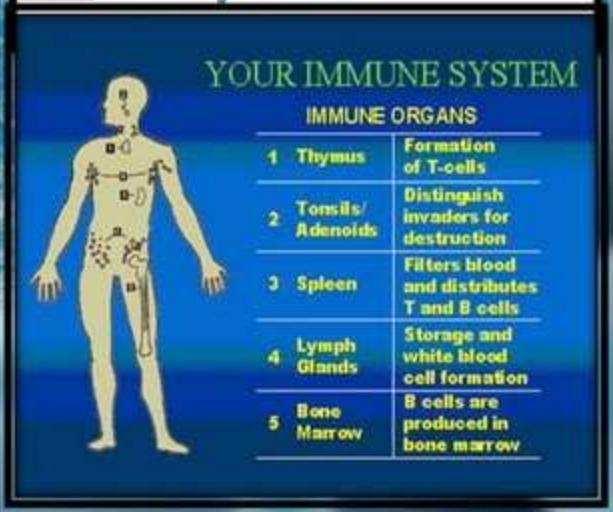
The Immune Response - why and how ?

- **Discriminate**: Self / Non self
- **Destroy**:
  - Infectious invaders
  - Dysregulated self (cancers)
- **Immunity**:
  - Innate, Natural
  - Adaptive, Learned




Thymus
Hormones
Complement System
Antibodies
Human Body Immune Systems
Lymphatic System
White Blood Cells
Spleen
Bone Marrow


THE IMMUNE SYSTEM
BONE MARROW
Intestinal tissue, liver, etc.
Lymphocytes
Thymus
Special Defense
Complement system
General Defense
Monocytes
Feeding cells
macrophage
granulocytes
B-lymphocytes
suppressor cells
plasma cells
antibodies
T-lymphocytes
killer cells
helper cells
complement factors
bacterium (foreign invader)


YOUR IMMUNE SYSTEM
IMMUNE ORGANS
1 Thymus
Formation of T-cells
2 Tonsils/ Adenoids
Distinguish invaders for destruction
3 Spleen
Filters blood and distributes T and B cells
4 Lymph Glands
Storage and white blood cell formation
5 Bone Marrow
B cells are produced in bone marrow

COMPONENTS OF IMMUNE SYSYTEM

- 2 major components of the immune system:
  - INNATE IMMUNE RESPONSE
    - ✓ first line of defense against an antigenic insult.
    - ✓ It Includes
    - ✓ Physical – skin, mucus membrane
    - ✓ Biochemical – complement, lyzosyme, interferons
    - ✓ Cellular – macrophages, neutrophils
  - ADAPTIVE IMMUNE RESPONSE
    - Humoral immunity - Antibody production – killing extracellular organisms.
    - Cell mediated immunity – cytotoxic / killer T cells – killing virus and tumour cells.

Who are involved ?

- Innate
  - Complement
  - Granulocytes
  - Monocytes/macrophages
  - NK cells
  - Mast cells
  - Basophils
- Adaptive:
  - B and T lymphocytes
  - B: antibodies
  - T : helper, cytolytic, suppressor.

COMPONENTS OF IMMUNE SYSTEM

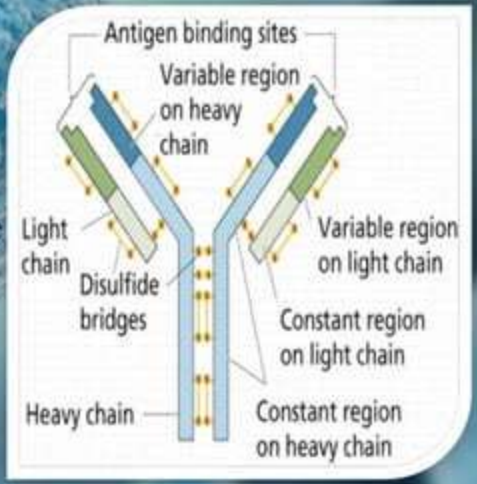
Antigens

- A substance that when introduced into the body, stimulates the production of an antibody.
- An antigen is an organic compound - protein, polysaccharide or glycolipid. It has 2 parts
- Hapten
- Carrier

- Antigens include:
- Toxins
- Bacteria
- Foreign blood cells
- Microorganisms
- Allergens
- Viruses Etc.

Antibodies

- They are gamma globulins or immunoglobulin's produced in the serum on exposure to antigen.
- Chemically they are glycoprotein's containing two heavy chains and two light chains joined together by disulfide bonds.
- It has 2 parts
  1) Fab
  2) Fc
- The entire antibody structure can be cleaved by papain(a proteolytic enzyme
- There are 5 types of Antibodies:
  IgG ,IgM , IgA , IgE , IgD



MECHANISM OF IMMUNE RESPONSE

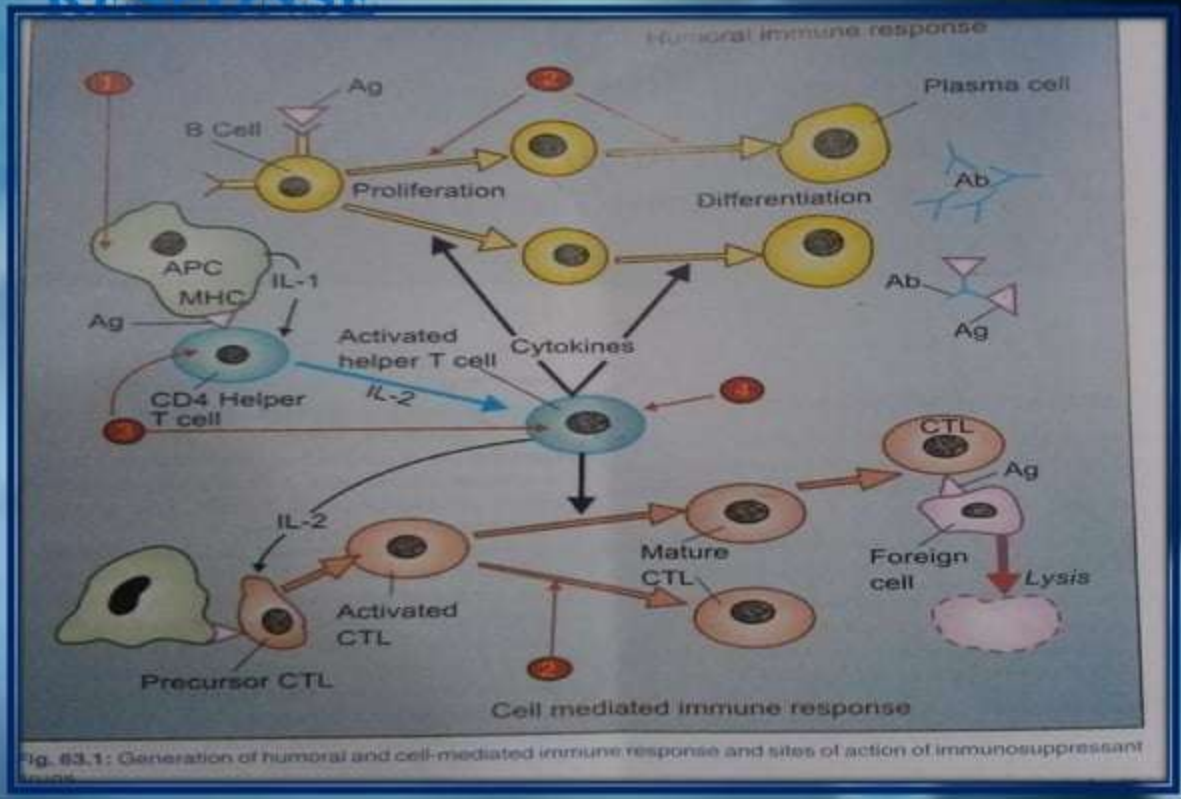


Fig. 63.1: Generation of humoral and cell-mediated immune response and sites of action of immunosuppressant

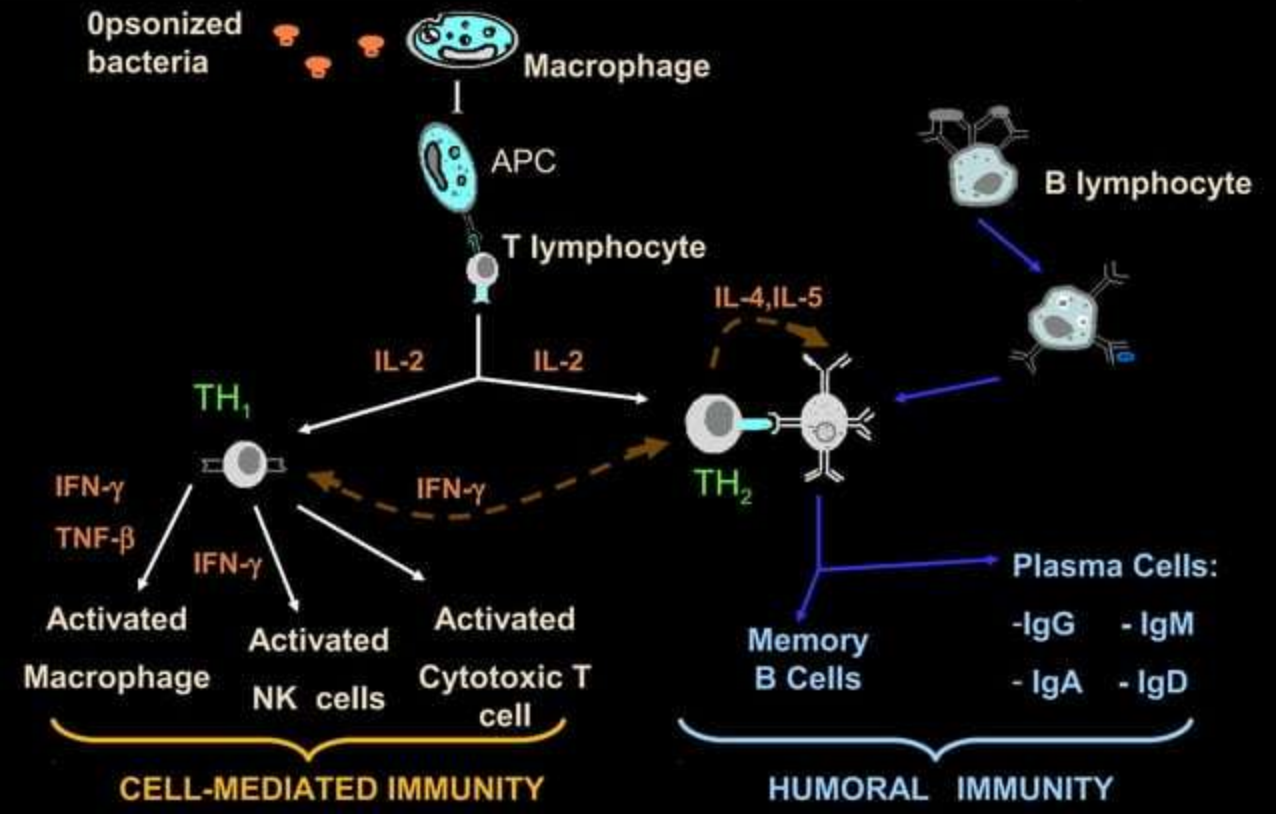
Humoral Immune Response- Antibodies

- The antigen is processed by macrophages or APC combined with class 2 MHC and presented to the CD4 helper cell. These are activated by interleukin *I.* proliferate and secrete cytokines. These in turn promote proliferation and differentiation of antigen activated B- cells into antibody secreted plasma cells. Antibody finally binds and inactivates the antigen

Cell Mediated Immune Response-T- lymphocytes

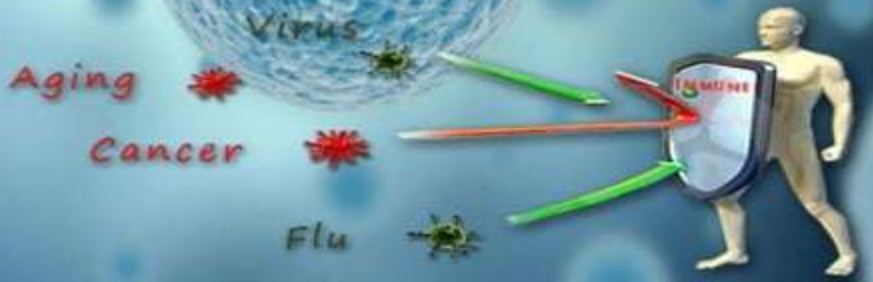
- Foreign antigen is processed and presented to CD4 Helper T cells which elaborate IL-2 and other Cytokines that in turn stimulate proliferation and maturation of precursor cytotoxic lymphocytes(CTL) that have been activated by antigen presented with class I MHC . The mature CTL recognizes cell carrying the antigen and lyse them.

IMMUNOPHARMACOLOGY



THERAPIES IN IMMUNOPHARMACOLOGY

- Immunomodulators
- Immunosuppressant's
- Immunostimulants



IMMUNOMODULATORS

Immunomodulators are drugs which either suppress the immune system – **Immunosuppressants**

or

stimulate the immune system – **Immunostimulants**

IMMUNOSTIMULANTS OR IMMUNOENHANCERS

- Immunostimulants are biologic therapeutic agents designed to boost the body's natural defenses to fight the cancer and other diseases.
- It uses materials either made by the body or in a laboratory to improve, target, or restore immune system function.
- Precisely, It is the use of medicines to stimulate a patient's own immune system to recognize and destroy cancer cells more effectively.
- Immunostimulatory drugs have been developed with applicability to infection, immunodeficiency,
- They works on cellular as well as humoral immune system or both

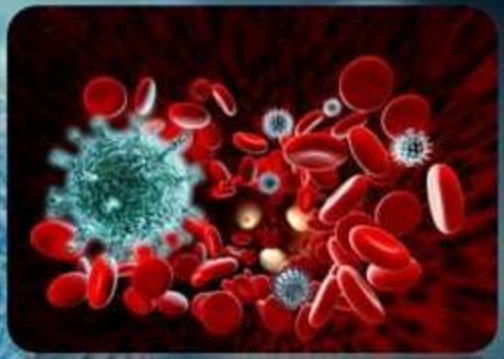
CLASSIFICATION

- Specific immunostimulants provide antigenic specificity in immune response, such as vaccines or any antigen.

Non-specific immunostimulants act irrespective of antigenic specificity to augment immune response of other antigen or stimulate components of the immune system without antigenic specificity, such as adjuvants and non-specific immunostimulators.

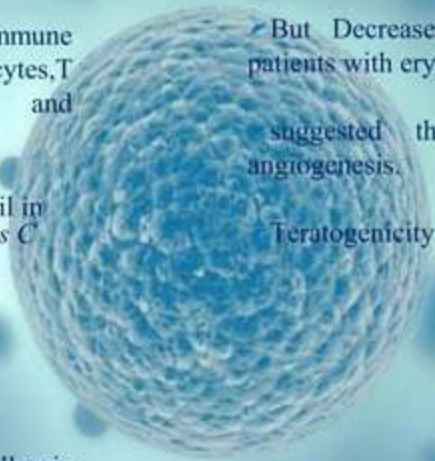
IMMUNOSTIMULANTS

1.Levamisole
2.Thalidomide
3.Isoprinosine
4.Immunisation
- ✓Vaccines
- ✓Immunoglobulins (Rho Ig)
- ✓Bacillus Calmette-Guerin (BCG)
- ✓Recombinant Cytokines



LEVAMISOLE:

- Levamisole was synthesized originally as an anthelmintic /antiparasitic agent
- But it restores the depressed immune function of B lymphocytes,T lymphocytes, monocytes and macrophages
- potentiate action of fluorouracil in adjuvant therapy of *Dukes class C colorectal CA*
- other uses:
- hodgkin's lymphoma
- RA
- ADR: Flu-like symptoms, allergic manifestation, nausea and muscle pain



THALIDOMIDE:

- Increases TNFα in patients who are HIV-seropositive.
- But Decreases circulating TNFα in patients with erythema nodosm leprosum
- suggested that the drug affects angiogenesis.
- Teratogenicity is an undesirable effect.

Immunisation
Vaccines and immunoglobulins (Rho Ig)

BACILLUS CALMETTE-GUERIN (BCG)

- Live culture of Bacillus Calmette-Guerin strain of *Mycobacterium bovis*.
- Induces granulomatous reaction at the site of administration.
- Therapeutic uses:

▪Treatment and prophylaxis of carcinoma of the urinary bladder.

▪prophylaxis of primary and recurrent stage of papillary tumors

- Adr : Hypersensitivity, shock, chills, fever, malaise,

RECOMBINANT CYTOKINES

- *Interferon gamma-1b*
- a recombinant polypeptide that activates phagocytes
- induces the generation of oxygen metabolites that are toxic to a number of microorganisms.
- *Interferon beta-1a* : 166-amino acid recombinant glycoprotein
- *interferon beta-1b* :165-amino acid recombinant glycoprotein
- Both have antiviral and immunomodulatory properties

CYTOKINES

- Interferons
- Interferons-alpha

- hairy cell leukemia
- chronic myelogenous leukemia
- malignant melanoma
- Kaposi's sarcoma
- anticancer → renal cell CA, carcinoid syndrome, T cell leukemia

CYTOKINES

Interferon-beta	Relapsing type multiple sclerosis
Interferon-gamma	Chronic granulomatous disease
Interleukin-2	Metastatic renal cell CA Malignant melanoma
TNF-alpha	Malignant melanoma Soft tissue sarcoma of extremities
Interferons & IL-2	(+) effects in response to Hep B vaccine
GM-CSF	Melanoma and Prostate cancer

RECENT THERAPEUTIC ADVANCES

1. Metastatic Melanoma

PHASE Zero

IMIQUIMOD (ZYCLARA)

➢A drug in the form of cream which stimulates a local immune response against skin cancer cells in sensitive areas on the face.
➢some doctors may use imiquimod if surgery might be disfiguring.

➢CYTOKINES

➢Cytokines such as INTERFERON-ALFA AND INTERLEUKIN-2 (IL-2), are proteins in the body that boost the immune system.
➢They are given as intravenous (IV) infusions, at least at first.
➢Interferon-alfa can be used as an added (adjuvant) therapy after surgery to try to prevent the thicker cells from spreading and growing. This may delay the recurrence of melanoma

BACILLE CALMETTE-GUERIN (BCG) VACCINE

➢BCG activate the immune system.
➢The BCG vaccine works like a cytokine by enhancing the entire immune system.
➢It is sometimes used to help treat stage III melanomas by injecting it directly into tumors.

LATER PHASES

CTLA-4 INHIBITOR

➢DRUG USED
•Ipilimumab (Yervoy)
➢It is another drug that boosts the immune response, but it has a different target.
➢It blocks CTLA-4, another protein on T cells that normally helps keep them in check.
➢Used in melanomas which can't be removed by surgery.
➢It helps in prolonging the life span of the patient

LATER PHASES

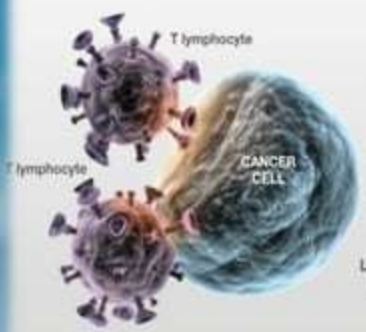
PD-1 INHIBITORS

➢DRUGS USED
•Pembrolizumab (Keytruda)
•Nivolumab (Opdivo)
➢These are drugs that target PD-1, a protein on immune system cells called *T cells* that normally help keep these cells from attacking other cells in the body.
➢By blocking PD-1, these drugs boost the immune response against melanoma cells, which can often shrink tumors and help people live longer

This is how the new immunotherapy for cancer works

1. Normal work of the immune system

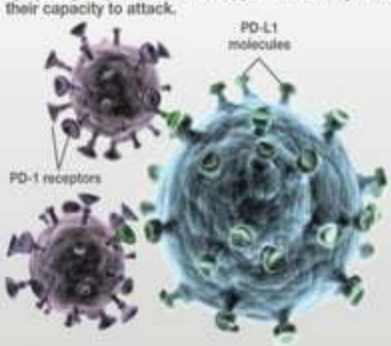
T lymphocytes are the cells of the immune system that identify tumour cells and destroy them.



Lymphocytes prevent the tumour from developing.

2. Camouflage of tumour cells

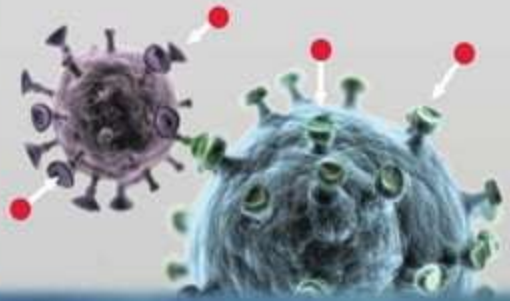
Some tumour cells arm themselves with a shield of molecules called PD-L1. Lymphocytes possess PD-1 receptors which, by bonding to these traps, destroy their capacity to attack.



The tumours become invisible to our defences and they spread.

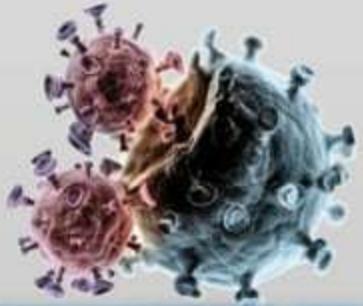
3. Action of the new inhibitor drugs

The new drugs based on antibodies block PD-1 from the cells of the immune system and PD-L1 from tumour cells to prevent their fatal action.



4. Result of immunotherapy

Lymphocytes, once freed from their blindness by the drug, regain their defence potential. They recognise cancer and reduce it.



This treatment, although still in its experimental stage, has had preliminary results on lung, kidney and skin cancers.

IMMUNOTHERAPY	CHEMOTHERAPY
• Utilizes body's own immune system to fight disease	• Kills Cancer cells directly
• Drugs act on immune system so they don't harm any other organ or cellular tissue	• Damages surrounding tissues
• Less potential treatment but has very less side effects	• More potential treatment but has more side effects
• It prolongs the life span	• Quicker results as compared to immunotherapy

✓ Radiation can be more targeted than chemotherapy. It can still damage surrounding cellular tissue, as it lacks the ability to differentiate between healthy and cancerous tissue.

✓ One way of decreasing the side effects of radiation and chemotherapy as well as boosting the effectiveness of treatment could be combination therapies with immunotherapy techniques. While the radiations & chemotherapy give quicker results; while immunotherapy boosts the immune system thus preventing the damage of healthy cells & prolongs the life span.

2. **INFLAMMATORY BOWEL DISEASE (IBD)**
   - i.e. Crohn's disease (CD) and ulcerative colitis (UC)
   - AZATHIOPRINE (AZA),
   - 6-MERCAPTOPURINE (6-MP),
   - METHOTREXATE (MTX)

3. **PANCREATIC CANCER**
   - Urelumab

4. **NON-SMALL CELL LUNG CANCER**
   - Ipilimumab

5. **ALLERGIC DISEASES**
   - Peptides

RECENT TECHNOLOGIES

✓Oncolytic Virus Therapies

Oncolytic virus therapy uses a modified virus that can cause tumor cells to destruct and generate a greater immune response against the cancer.

In May 2015, based on results from a large, completed phase III trial, the oncolytic virus therapy **TALIMOGENE LAHERPAREPVEC (T-VEC),** made by Amgen, was recommended for marketing approval by an independent advisory panel to the FDA; final approval from the FDA itself is pending. A phase II study to test **T-VEC** in patients with unresected, stage 3 or 4 melanoma, is currently open ( )

✓Adoptive T Cell Therapy

Another major avenue of immunotherapy for melanoma is ADOPTIVE T CELL TRANSFER. In this approach, T cells are removed from a patient, genetically modified or treated with chemicals to enhance their activity or numbers, and then re-introduced into the patient with the goal of improving the immune system's anti-cancer response.

✓Therapeutic Vaccines

Cancer vaccines are designed to elicit an immune response against tumor-specific or tumor-associated antigens, encouraging the immune system to attack cancer cells bearing these antigens.

✓Several additional checkpoint inhibitors, and checkpoint inhibitor combinations

A phase IIb trial to test the **HyperAcute-Melanoma vaccine (dorgenmeltucel-L)** and ipilimumab in patients with melanoma ( )

MPDL3280A, an anti-PD-L1 antibody, is being tested in numerous cancers in a phase I trial ( ) and a phase I trial in melanoma ( ).

IMMUNOSUPPRESSANT DRUGS

- These are drugs which inhibit cellular/humoral or both immune response
- Major use in organ transplantation and autoimmune diseases

Classification of immunosuppressants

1 . Calcineurin inhibitors (SpecificT-cell inhibitors)
   - Cyclosporine (Ciclosporin), Tacrolimus

2. Antiproliferative drugs (Cytotoxic drugs)
   - Azathioprine, Cyclophospharnide,
   - Methotrexate, Chlorambucil,
   - Mycophenolate mofetil (MMF)

3. Glucocorticoids
   - Prednisolone and others

4. Antibodies
   - Muromonab CD3, Antithymocyte globulin(ATG),
   - Rho (D) immuneglobulin

MOA of immunosuppressant drugs

- Cyclosporine and Tacrolimus inhibit antigen stimulated activation and proliferation of a helper T cells as well as expression of IL-2 and other cytokines by them
- Cytotoxic drugs block proliferation and differentiation of T and B cells .
- Glucocorticoids inhibit MHC expression and IL-I. IL –II. IL-6 production so that Helper T cells are not activated.
- Antibodies like muromonab CD-3 , antithymocyte globulyne specifically bind to helper Tcells and prevent their response and deplete them

Calcineurin inhibitors (Specific T-cell inhibitors)

- Cyclosporine is a cyclic polypeptide with 11 amino acids, obtained from a fungus
- Highly selective immunosuppressant
- Used in organ transplantations.
- Selectively inhibits T lymphocyte proliferation, IL-2 and other cytokine production

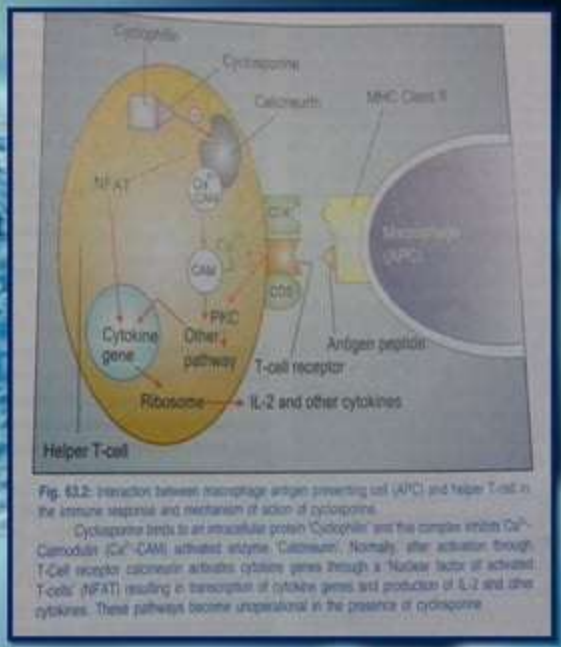


Fig. 63.2: Interaction between macrophage antigen presenting cell (APC) and helper T-cell in the immune response and mechanism of action of cyclosporine.

Cyclosporine binds to an intracellular protein 'Cyclophilin' and the complex inhibits Ca^{2+}-Calmodulin (Ca^{2+}-CAM) activated enzyme 'Calcineurin'. Normally, after activation through T-Cell receptor calcineurin activates cytokine genes through a 'Nuclear factor of activated T-cells' (NFAT) resulting in transcription of cytokine genes and production of IL-2 and other cytokines. These pathways become unoperational in the presence of cyclosporine

- Blocks T-cell activation
- Binds to cyclophillin → inhibits *calcineurin* activity → inhibits gene transcription of IL-2, IL-3, IFNγ & other factors
- Most commonly used immunosuppresant for renal transplantation
- Indications:
  - ✓ transplant rejection (kidney, liver, pancreas, cardiac)
  - ✓ Autoimmune disorders (uveitis, RA, DM type1)
- Toxicities:
  - ✓ nephrotoxicity, hyperglycemia, hyperlipidemia, osteoporosis, ↑ hair growth, transient liver dysfunction

TACROLIMUS (FK506)

- Binds to FK-binding protein → inhibits T-cell activation
- 10-100 times more potent than cyclosporine
- Liver & kidney transplant
- Oral or IV : $t_{1/2}$ = 9-12 hrs
- Toxicity:
  - nephrotoxicity, neurotoxicity, hyperglycemia, GI dysfunction

CYTOTOXIC DRUGS

- Preventing clonal expansion of T and B lymphocytes, **Azathioprine**
- Purine antimetabolite, its selective uptake into immune cells and intracellular conversion to the active metabolite 6-mercaptopurine, which then undergoes further transformations to inhibit purine synthesis and damage to DNA.
- It selectively affects differentiation and function of Tcells and inhibits cytolytic lymphocytes;
- prevention of renal and other graft rejection but it is less effective than cyclosporine used in patients developing cyclosporine toxicity.
- It has also been used in progressive rheumatoid arthritis and some other autoimmune diseases.

IMMUNOPHARMACOLOGY

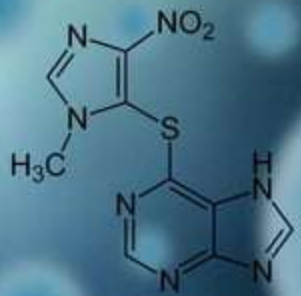
CYTOTOXIC Agents:

1. Azathioprine
2. Leflunomide
3. Cyclophosphamide

Azathioprine

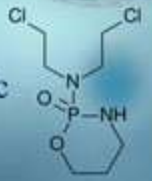
- Metabolized to 6-mercaptopurines
- Inhibit purine synthesis→ interferes with nucleic acid metabolism → inhibits cellular & humoral responses
- Highly teratogenic
- Well absorbed from GI tract
- Renal allograft, AGN, SLE(renal), RA, Crohn's disease
- Prednisone-resistant antibody-mediated ITP
- Autoimmune hemolytic anemia

- Toxicities:
  - Bone marrow suppression
  - GI disturbances: N&V, diarrhea
  - Skin rashes, drug fever, hepatic dysfunction



Cyclophosphamide

- Cytotoxic drug effective on B cells.
- used in bone marrow transplantation
- In rheumatoid arthritis, it is rarely used, only when systemic manifestations are marked.
- Most potent immunosuppressive drug
- Destroys proliferating lymphoid cells
- Autoimmune disorders: SLE
- Acquired factor XIII antibodies
- Bleeding syndromes
- Toxicities:
  - Pancytopenia, hemorrhagic cystitis



Chlorambucil

- weak immunosuppressant
- Used in autoimmune diseases.

Methotrexate

- This folate antagonist is a potent immunosuppressant which markedly depresses cytokine production and cellular immunity, and has antiinflammatory property.
- It has been used as a first line drug in many autoimmune diseases like rapidly progressing rheumatoid arthritis, severe psoriasis, pemphigus (skin blistering disease), myasthenia gravis, uveitis, chronic active hepatitis.

Mycophenolate

- New immunosuppressant prodrug of mycophenolic acid which selectively inhibits inosine monophosphate dehydrogenase enzyme essential for synthesis of guanosine nucleotides in the T and B cells .
- Lymphocyte proliferation, antibody production and cell-mediated immunity are inhibited.
- As 'add on' drug to cyclosporine + glucocorticoid in renal transplantation,
- Vomiting, diarrhoea, leucopenia g.i. bleeds are t… adverse eff…

GLUCOCORTICOIDS

- Inhibit MHC expression proliferation of T lymphocytes and suppress all types of hypersensitization and allergic phenomena.
- Greater suppression of CMI in which T cells are primarily involved, e.g. delayed hypersensitivity and graft rejection-basis of use in autoimmune diseases and organ transplantation.
- Factors involved may be inhibition of IL-1 release from macrophages; inhibition of lL-2 formation and action + T cell proliferation is not stimulated; suppression of natural killer cells, etc

USES -

- Transplant rejection
- Autoimmune diseases – RA, SLE, Hematological conditions
- Psoriasis
- Inflammatory Bowel Disease

CORTICOSTEROIDS

- MOA:
  - inhibit T-cell proliferation & T-cell dependent immunity
  - Inhibit expression of genes encoding cytokines
  - Inhibit production of inflammatory mediators
- Affects cell-mediated immunity more than humoral immunity
- Continuous administration:
  - ↑ fractional catabolic rate of IgG
- Indications:
  - Autoimmune disorders
    - autoimmune hemolytic anemia, LE
    - ITP, Inflammatory Bowel Dse,, Hashimoto's
  - Modulate allergic reactions - asthma
  - Organ transplantation – rejection crisis

Corticosteroids

- Immunosuppressive dose:
  - 10-100 mg/day
- Adverse effects:
  - GI bleeding
  - adrenal suppression
  - fluid retention
  - diabetes
  - proximal muscle wasting
  - superinfections

SIROLIMUS (RAPAMYCIN)

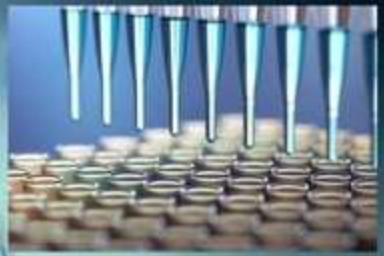
- Binds also to immunophyllin → blocks the response of T cell to cytokines
- Potent inhibitor of B-cell proliferation & Ig production
- Indications:
  - Kidney & heart allografts
  - C syclosporin → psoriasis & uveoretinitis

INTERFERONS

- Type 1: induced by viral inf.
  - ✓ IFN-alpha → prod. by leukocytes
  - ✓ IFN-beta → fibroblasts & epithelial cells
- Type 2: IFN-gamma → produced by activated T-lymphocytes
- Indications: cancer
- IFN-β → multiple sclerosis
- IFN-γ →chronic granulomatous disease

Antibodies as Immunosuppressive Agents

- Antilymphocytic antibody
- Immune Globulin IV
- Hyperimmune Immunoglobulins
- Monoclonal Antibodies
- Rh (D) Immune Globulin Micro-Dose
  - Prevention of hemolytic disease of the newborn
  - Given to mother within 72 hrs after delivery of an Rh-negative baby



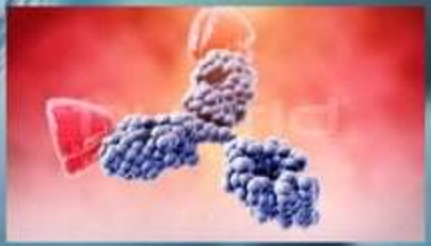
MONOCLONAL ANTIBODIES

1.Muromonab- CD3

2. Palivizumab

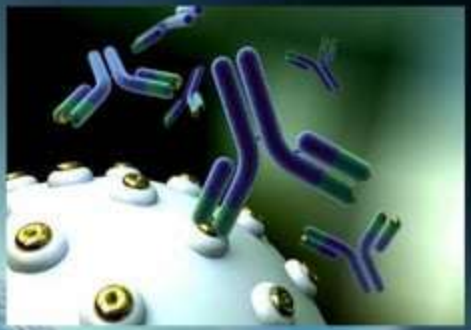
3. Rituxumab

4. Trastuzumab



Muromonab-CD3

- A T-cell specific antibody
- Renal transplantation, heart / renal

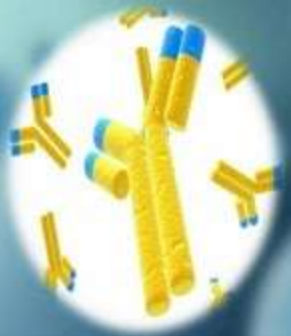


Palivizumab

- RSV

Rituximab

- Follicular B-cell non-Hodgkin's lymphoma



Trastuzumab

- metastatic breast CA

Immunosuppression in organ transplantation

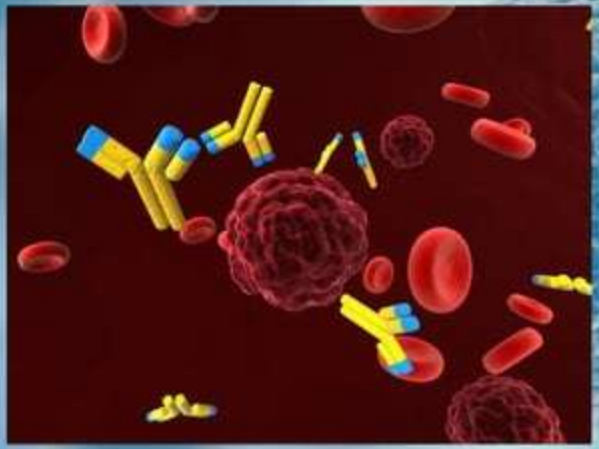
- Induction regimen
- Maintenance regimen
- Antirejection regimen

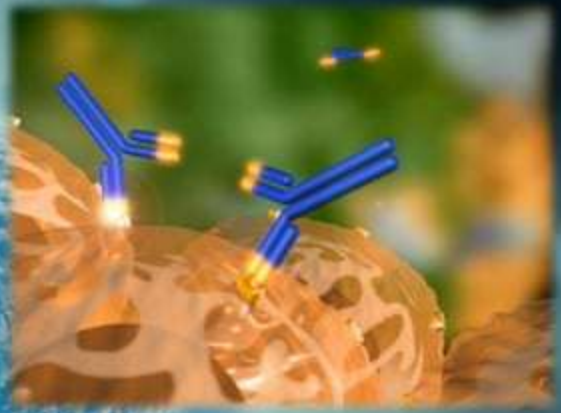
ADVERSE EFFECTS OF IMMUNOSUPPRESSANT THERAPY

a) Increased risk of bacterial, fungal, viral as well as opportunistic infections.

b) Development of lymphomas and related malignancies after a long latency.

AUTOIMMUNITY

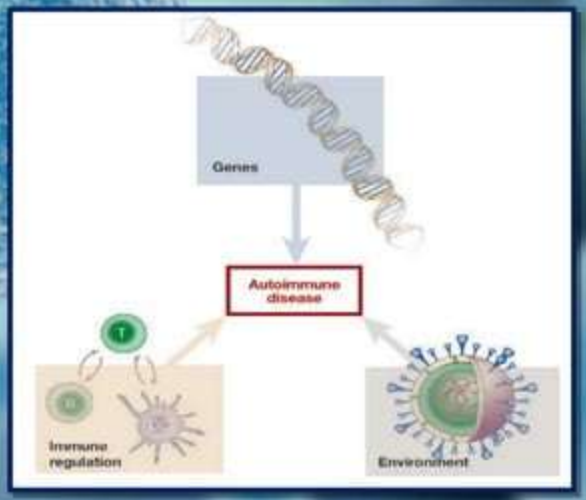


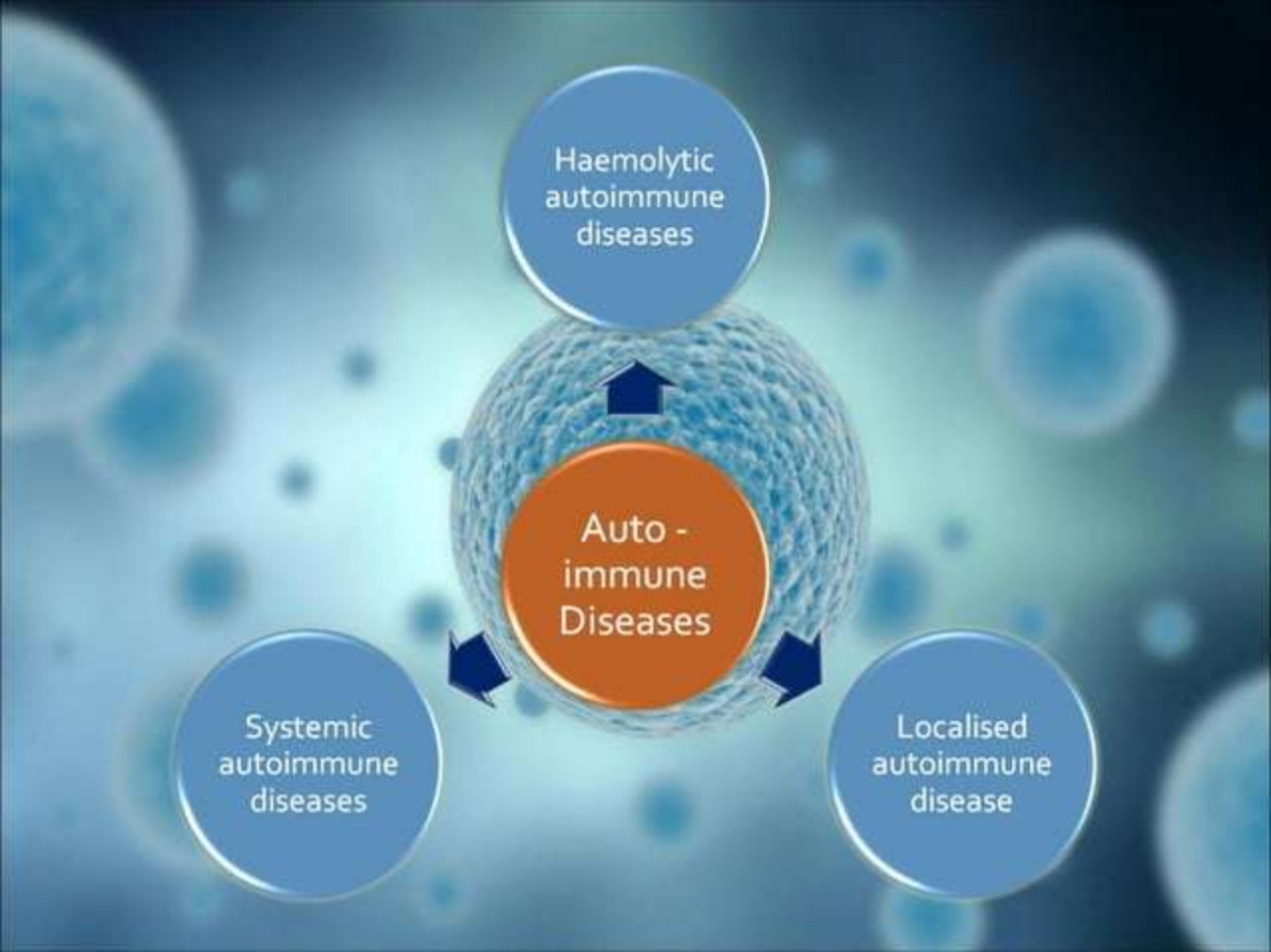


Introduction

- Autoimmune diseases is a group of disorders in which tissue injury is caused by humoral (by auto-antibodies) or cell mediated immune response (by auto-reactive T cells) to self antigens.
- An autoimmune disorder may result in:
- The **destruction** of one or more types of body tissue
- **Abnormal growth** of an organ
- **Changes** in organ function

CAUSES




Haemolytic autoimmune diseases
Auto - immune Diseases
Systemic autoimmune diseases
Localised autoimmune disease

1. Haemolytic autoimmune diseases

- Clinical disorder due to destructions of blood components. Auto Ab are formed against one's own RBCs, Platelets or Leucocytes .

- E.g. Haemolytic anaemia, Leucopenia, Thrombocytopenia, etc.

2. Localised autoimmune disease

- A particular organ is affected due to auto Abs.
- For example:
  - **Thyroiditis** (attacks the thyroid)
  - **Multiple sclerosis** (attacks myelin coating of nerve axons)
  - **Myasthenia gravis** (attacks nerve-muscle junction)
  - **Juvenile diabetes** or Type I DM (attacks insulin-producing cells)

3. Systemic autoimmune disease

- Non organ-specific autoimmune diseases
- Immune complexes accumulate in many tissues and cause inflammation and damage.
- For example:
  - **Systemic lupus Erythematosus** (anti-nuclear Ab.): Harms kidneys, heart, brain, lungs, skin.
  - **Rheumatoid Arthritis** (anti-IgG antibodies): Joints, hearts, lungs, nervous system.
  - **Rheumatic fever:** cross-reaction between antibodies to streptococcus and auto-antibodies.

TREATMENT

- The key to treating autoimmunity is immunomodulation .
- Some autoimmune diseases are treated with medications that enhance specific symptoms.
- **Hemolytic anaemia**: Treated with Vit B_{12}
- **SLE** : Treated with nonsteroidal anti-inflamatory drugs such as ibuprofen or naproxen, antimalarial drugs, and corticosteroids.
  - In more aggressive cases, immunosuppressive drugs may be used.

IMMUNOTHERAPY – AN INTERNAL AID FOR TREATMENT OF DISEASES


THANK YOU
THANK YOU
FOR YOUR
TIME