PC
Pharmacology Concepts
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Immunomodulators

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Pharmacology 3

IMMUNOSUPRESSANT DRUGS

Drugs, which inhibit the Cellular/Humoral or both type of immune response. They are majoraly used in Organ Transplantation and Autoimmune Disorders.

CLASSIFICATION

1. Calcineurin Inhibitors :- Cyclosporine, Tacrolimus

"Calcineurin - Ca^{2+} dependent Enz (Serine/Threonine Phosphatase) $\xrightarrow{(+)}$ Cell-mediated Immune Response

2. mTOR Inhibitors - Sirolimus, Temsirolimus, Everolimus

mTOR - mammalian Targeted of Rapamycin that promotes the proliferation & differentiatn of T-Cell

3. Antiproliferatives - Azathioprine, MTX, Cyclophosphamide, Chlorambucil

4. Glucocorticoids - Prednisolone
- Inhibit the MHC expression & activatn of T lymphocyte
- Regulate the Expression of IL & Cytokine genes

Biological Agents

5. IL-1 Receptor Antagonist - Anakinra

Macrophages → IL-1 → (+) T helper Cell & induce productn of ILs & Metalloproteinase

use - Rheumatoid arthritis

6. IL-2 Receptor Antagonist - Basiliximab, Daclizumab
- These are the CD-25 antibodies that block the IL-2 receptor & ↓ the binding of CD-25 on IL-2 R & arrest the activated T cell.

7. TNFα Inhibitors - Etanercept, Adalimumab Infliximab

↳ TNFα - Selectively activates the macrophages & Immune cells by activatn of $TNFR_1$ & $TNFR_2$

8. Anti-CD3 Antibody - Muromunab CD3

↳ It is a murine monoclonal antibody, which acts against the CD-3 glycoprotein expressed near to T cell receptor on helper T cells

9. Polyclonal Antibody - Antithymocyte Antibody (ATG)
Rho(D) Immune globulin

ATG - Purified from horse or rabbit immunized with human thymic lymphocytes which contains antibodies against many CD antigens.

Anti(D) Immune globuline - It is human IgG having high titer of antibodies against Rh(D) Antigen, & does not allow them to induce antibody formation in Rh negative individuals.

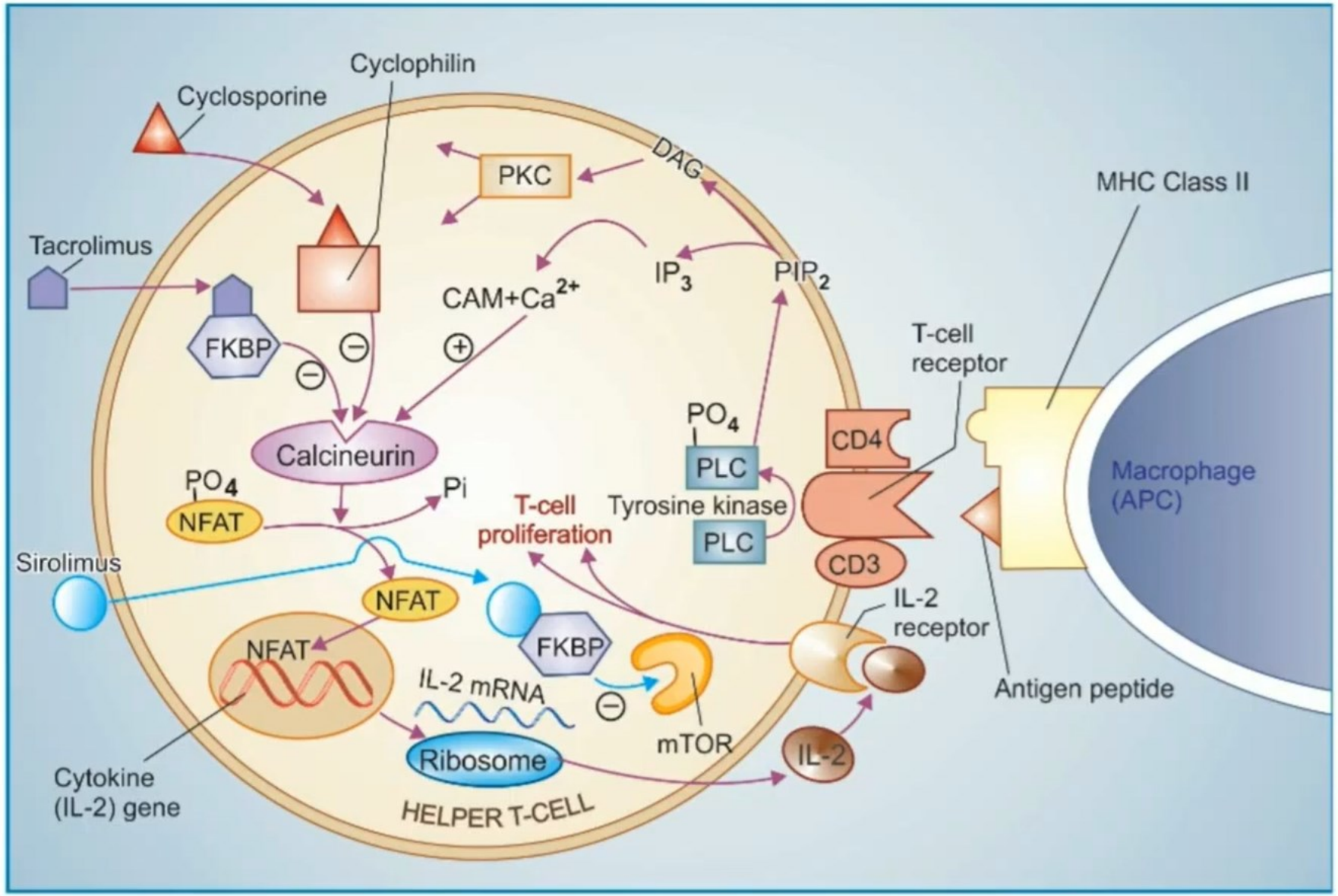


Fig. : Interaction between macrophage antigen presenting cell (APC) and helper T-cell in the immune response and mechanism of action of cyclosporine, tacrolimus and sirolimus.
Cyclosporine binds to an intracellular protein 'Cyclophilin' and this complex inhibits Ca2+-Calmodulin (Ca2+-CAM) activated phosphatase 'Calcineurin'. Tacrolimus also inhibits calcineurin, but after binding to a different protein FKBP (FK binding protein). Normally, after activation through T-cell receptor, calcineurin dephosphorylates a 'nuclear factor of activated T-cells' (NFAT) which translocates to the nucleus and triggers transcription of cytokine genes resulting in production of IL-2 and other cytokines. IL-2 diffuses out and acts on IL-2 receptor to stimulate T-cell proliferation and other processes, carrying forward the immune response.
Sirolimus also binds to FKBP, but this complex acts at a later stage. It binds to and inhibits a kinase termed m-TOR (mammalian target of rapamycin) which is a key factor for progression of cell proliferation.
PLC—phospholipase C; PIP2—phosphatidyl inositol bisphosphate; DAG—diacyl glycerol; PKC—protein kinase C.

Immunosuppressant Drugs (Part 1): Immune Responses and Mode of Action of Immunosuppressant drugs

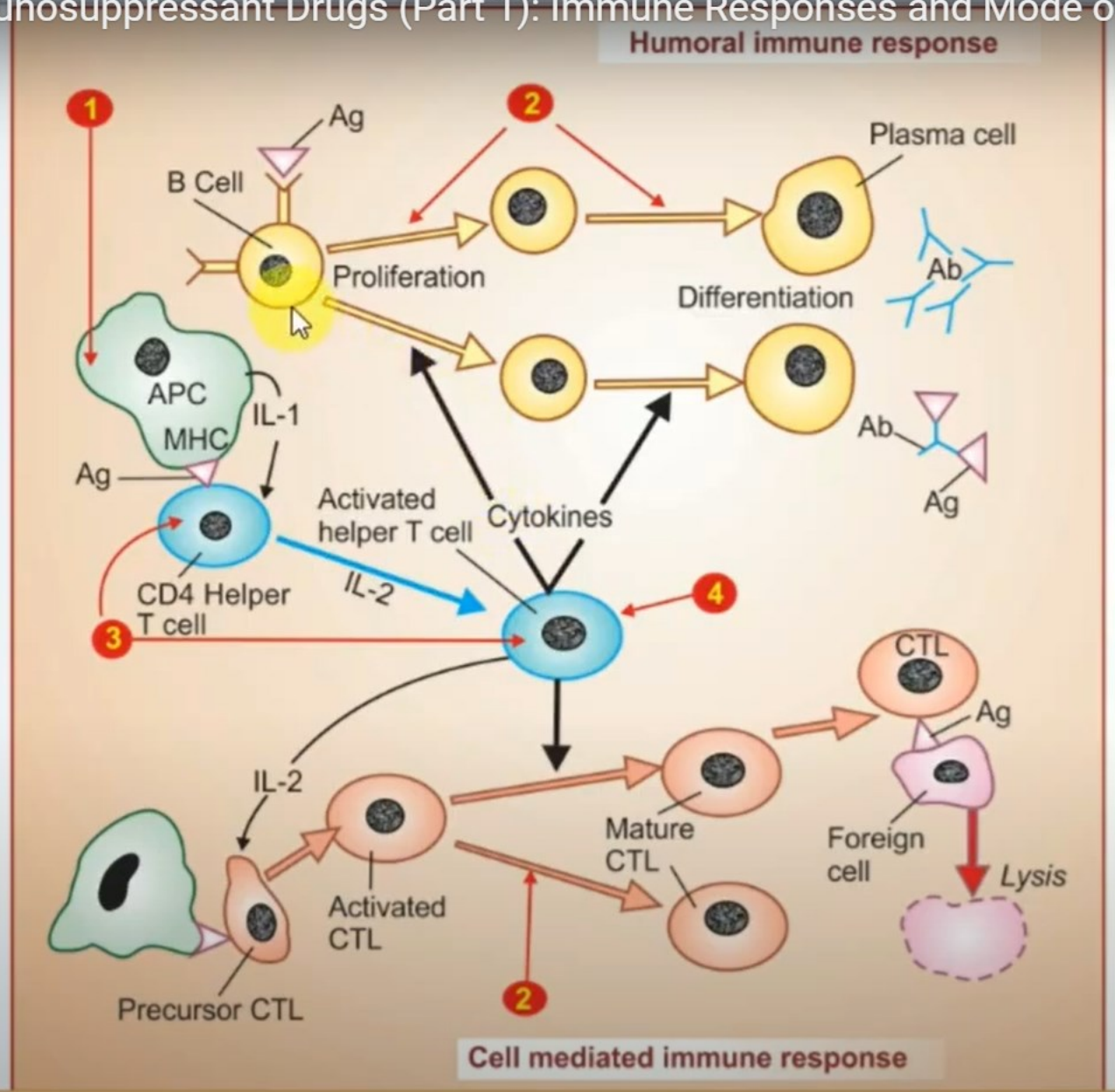


Fig: Generation of humoral and cell-mediated immune response and sites of action of immunosuppressant drugs

The antigen (Ag) is processed by macrophages or other antigen presenting cells (APC), coupled with class II major histocompatibility complex (MHC II) and presented to the CD4 helper T-cell which are activated by interleukin-I (IL-1), proliferate and secrete cytokines—these in turn promote proliferation and differentiation of antigen activated B cells into antibody (Ab) secreting plasma cells. Antibodies finally bind and inactivate the antigen.

In cell-mediated immunity—foreign antigen is processed and presented to CD4 helper T cell 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 (Killer cells) recognize cells carrying the antigen and lyse them.

1. Glucocorticoids inhibit MHC expression and IL-1, IL-2, IL-6 production so that helper T-cells are not activated.
2. Cytotoxic drugs block proliferation and differentiation of T and B cells.
3. Cyclosporine, tacrolimus and sirolimus inhibit antigen stimulated activation and proliferation of helper T cells as well as expression of IL-2 and other cytokines by them.
4. Antibodies like muromonab CD3, antithymocyte globulin specifically bind to helper T cells, prevent their response and deplete them.

CYCLOSPORINE/CICLOSPORINE

↳ It is a cyclic polypeptide with 11 amino acids, obtained from fungus, & introduce in 1977. Highly selective immunosuppressant & ↑ the sucess of Organ transplantation.

MOA:- It inhibits the calcineurin & dependent T lymphocyte proliferation, IL-2 & Cytokines production as well as response of inducer T cell to IL-1, without any effect on supressor T cell. Lymphocyte arrested in G_0 & G_1 phase

It also enhances the expression of TGF-β, an inhibitor of IL-2. Thus ↓ IL-2 mediated T cell Proliferation and productn of killer T cell (CLT)

Pharmacological actn & Uses -

It is most active when It administered before Antigen exposure,

It also supress the responses of primed helper T-cells; hence useful in Auto Immune Diseases

Major use in prevention of Graft Rejection in Organ Transplantation (selectively ↓ Cell mediated immunity)

It leaves the recipient with enough immunity to protect against bacterial infection, & Humoral immunity also intact.

Use 1. Organ Transplantatn - Kidney, Liver, Heart, Bone Marrow

2. Auto Immune dis → Rheumatoid Arthritis, Uveitis, Asthma, Inflammatory Bowel disease, Dermatomyositis

PKinetics:- In Organ transplantion, for induction it is started orally 12 hours before, and if graft rejection has started, it can be given by IV route due to low bioavailability depends on +nce of bile.

It is concentrated in WBCs & RBCs, Metabolised by Liver & excreted in bile

Plasma $t_{1/2}$ - biphasic - 4-6 h & 12-18 h

ADR:- # Nephrotoxicity, # Impaired Liver function, # ↑ BP, # Precipitation of Diabetes # Hyperkelaemia, # Hyperuricaemia, # Gum hyperplasia etc

Drug Interaction:- ① ↑ the Nephrotoxicity with Aminoglycoside, Vancomycin, Amphoterecin B, & NSAIDs

② Enz inducers (Phenytoin, Barbitone) - ↓ Effectiveness

③ Enz inhibitors (erythromycin) → ↑ toxicity

TACROLIMUS (FK506) - Macrolide derivetive

Tacrolimus + FKBP → ↓ Calcineurin dependent action

100 times more potent than cyclosporine

Therapeutic efficacy, Uses, & toxicity profile are similar to cyclosporine

Both drug required Therapeutic drug monitoring (TDM) for dose adustments.

It is Alternate to cyclophosphamide, but preffered in Liver transplantation (becouse absorbtion is not dependent on bile)

It is also used in Fistulating Crohn's disease

SIROLIMUS - m-TOR INHIBITOR

It is a newer & potent immunosupressant drug, is a macrolide antibiotic (similar as Tacrolimus)

MOA → Inhibit the IL-2 mediated T-Cell proliferation by blocking of mTOR (mammalian Target of Rapamycin)

IL-2 —(+)→ IL2R —Kinase mTOR→ T Cell proliferation

Sirolimus-FKBP —(−)→ Kinase mTOR

"↓ Cell mediated immunity"

Sirolimus arrest the immune response at later stage than Cyclosporin, and may be considered as an anti-proliferative agents

P'KINETICS :- # Absorbed orally (fatty meal ↓ absorption)

BA - 15-20% (highly metabolised by liver, Cyp3A4)

Excretion occurs mainly by biliary route

Plasma $t_{1/2}$ - 60 hours

Metabolic Enzyme inhibitor & inducer may alter the Plasma conc., so require TDM

Uses - # Prophylaxis & Therapy of Graft Rejection Reaction, used alone or along with lower dose of - Tacrolimus / Corticosteroids / Mycophenolate, & Cyclosporine*

→ stem cell transplantation

Sirolimus coated stents are being used to reduce the incidence of coronary artery stenosis, by inhibiting endothelial proliferation at the site

ADR :- # Bone Marrow Suppression (Thrombocytopenia)

↑ Serum Lipid, # Liver damage, # Diarrhoea

GLUCOCORTICOIDS

Potent Immunosuppressant & Anti inflammatory actn

They inhibit the -

- ↳ MHC expression
- ↳ Proliferation & Activation of T Lymphocyte
- ↳ Expression of IL & Cytokines

Marked Effect on Cell mediated than Humoral

Used, Combination with others or in maintence

IMMUNOSTIMULANTS

Immunostimulators are the substaces that stimulate the immune system by inducing activation or increasing of its components.

They can be – Biological Products (vaccines), Pharmaceuticals (drugs & natural drugs), & Cell based.

These are mainly used in infective diseases, immunodeficiency & cancer therapy.

Classification :- Two main Categories -

(A) Specific Immunostimulants – These are provide antigen Specificity in immune response, such as vaccine or any antigen. e.g., - Vaccines,

(B) Non-Specific – They enhance the immune responses of other antigen or stimulate components of immune system without antigenic Specificity.

e.g., # Biological Agents – Interleukins, Cytokins, Interferons, Colony Stimulating Factors

Drugs – Thalidomide, Levamisole,

Natural Products (Booster) → Multivitamin, Minerals (Zn, Se, Mg), Garlic, Ginseng, Green Tea, black Cumin, Licorice, etc

VACCINES

Type	Live	Killed
1. Bacterial –	BCG (TB)	cholerae, Typhoid Pertusis
2. Viral –	Small pox, Rubella, Measeles, Mumps Rotavirus	Influenzae Rabies
3. Rickettsial –		Typhus
4. Toxoids –	Diphtheria, Tetanus	

Immunization / Vaccination :-

Active immunization involves administration of an antigen (whole, killed, attenuate live organism) or specific peptide constituents of organism.

Booster dose can required in killed (Inactivated) org. vaccine

Vaccines are also developing for specific Cancer & auto immune disease

DNA Vaccine → For Infections & Cancer

Passive Immunization – Anti Sera / Antibodies

Immunization with specific Immuno globulin in Congenital or Acquired immunodeficiency.

e.g. – Hepatitis-B Immuno Globulin
Rho(D) immune Globulin

IMMUNOSTIMULANTS ⇒ VACCINES

1. Bacterial Vaccine :→ They contain killed or attenuated bacteria that activate the immune system. By immunization Antibodies are buildup against the particular bacteria & prevents this infect^{n} later.

e.g.,- BCG (TB), pneumococcal, Thyphoid, etc

2 Viral Vaccine :- They contain either inactivated or attenuated (Live but not capable of causing disease. The killed virus have loss their ability to replicate, but it contains more antigen than live vaccines & produce higher immune response.

e.g.,- Rotavirus, Rubella, Influenzae, etc

3. Therapeutic Vaccine :— Vaccines which are intended to treat or cure a disease by stimulating the immune system.

eg, - Therapeutic Cancer Vaccine -

Bacillus Calmette Guerin (BCG) → Originally developed for TB, & it is also approved for Bladder cancer. It contains attenuated live attenuated bacteria Mycobacterium boris. BCG can be administered intravesically direct to bladder as adjuvant in other cancer Vaccine. They attract immune cells that kill cancer

HPV Vaccine # Hep.-B Vaccine — Cervical, Liver

Sipuleucel-T → prostate Cancer

4. Combination Vaccine -

Merge the antigens to prevent multiple strain of infective agents causing the same infection. And it can be also prevent agains multiple disease.

e.g. DPT = Diphtheria, Pertusis, Typhoid

Twinrix → Hep A & Hep B

Pediarix → DTaP, Hep B & IPV (Polio)

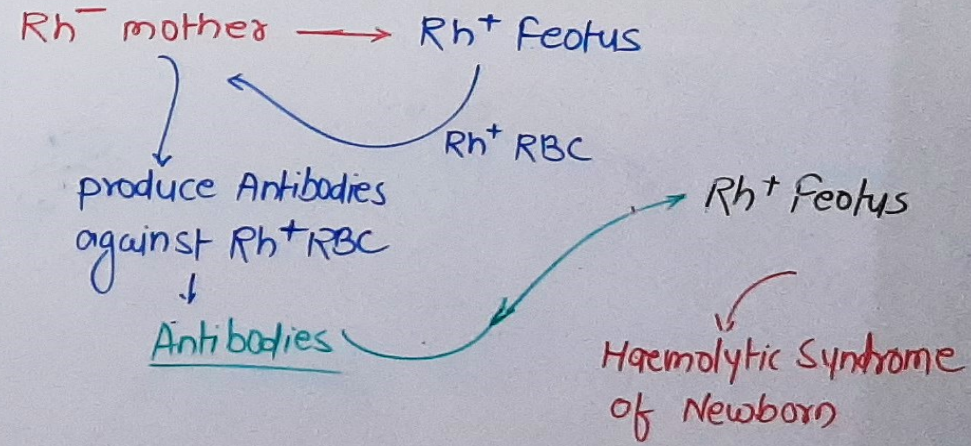
Kinrix - DTap & IPV

IMMUNO GLOBULIN

Rho(D) Immuno Globulin = (Anti D)

It consist of Ig G containing a high titer of antibodies against the Rho(D)/Rh antigen on the surface of RBCs

MOA - Rho(D) Ig (Antibodies) + Rho(D) Antigen → Neutralise or prevent sensetization of Rh^{-} Woman



IMMUNOSTIMULANTS

INTERLEUKINS :- ILs are group of Cytokines which synthesized by lymphocytes, monocytes, & macrophages. They regulate Immune System by →

↳ T-Cells & B-cells proliferation

↳ Activation of Killer T Cell,

Ag → (+) Helper T cell Receptor → IP_3/DAG (+)→ Ca-Cam

NFAT-P ↓(+) Calcineurin

IL-2 gene transcriptn (+)← NFAT

IL-2 (+)→ IL-2R mTOR→ ↑ T-Cell proliferation

Cytokines → B-Cell proliferatn & NK cell activatn

e.g., - Human Recombinant → Aldesleukin, Oprelvekin

Mainly used in Cancer Therapy

INTERFERON :- Interferons (α, β, γ) are the cytokines produced by host-cells in response to viral infection

They have also immunomodulatory & antiproliferative activity. They bind with cell surface receptor & activate series of intracellular events -

↳ (+) Enzyme ↳ ↓ cell proliferation

↳ ↑ Immune response by → (+) NKCell, (+) Macrophages

↳ e.g., - Recombinant - Interferon α-2b,

use - hairly cell leukemia, melanoma, AIDS-related kaposi sarcoma

R. Inf γ 1b - used in chronic granulomatous dis

R. Inf β 1a - used in multiple sclerosis

COLONY STIMULATING FACTOR

These are the glycoproteins that promote production of WBC (Neutrophil), in response to infection

Colony stimulating factors (+)→ Stem Cell (Bone Marrow) → ↑ Production of WBC

use → in Neutropenia condition under Cancer

LEVAMISOLE - was synthesized originally as an Anthelmintic but appears to "restore depress immune function of B Lymphocyte, Monocyte, Macrophages & T-Lymphocyte"

use- used as an adjuvant therapy with Anticancer drugs (5FU) to avoid bone marrow suppression & Agranulocytosis

THALIDOMIDE :- uses in Erythema nodosum leprosum & Multiple myeloma

↳ Never Use pregnant Woman

↳ Sever Birth Defect

↳ Teratogenic Drug