IMMUNOMODULATORS

What is Immunomodulation?

Immunomodulation is a therapeutic approach in which we try to intervene in auto regulating processes of the defense system.

Immunomodulators act via 2 mechanisms

- Immunosuppression
- Immunostimulation

Elements of the Immune System:

The Innate Immune System:

- First line of defense against an invading pathogen (antigen).
- It includes physical (e.g., skin), biochemical (e.g., complement, lysozyme, interferons), and cellular components (neutrophils, monocytes, macrophages, natural killer [NK], and natural killer-T [NKT] cells).

The Adaptive Immune System:

- Respond to a variety of antigens, each in a specific manner.
- Discriminate between foreign ("non-self") antigens (pathogens) and self antigens of the host.
- Respond to a previously encountered antigen in a learned way by initiating a vigorous memory response.

Autoimmunity

- Mechanisms proposed to explain autoimmunity:

➢ Exposure of self-reactive T lymphocytes to antigens previously sequestered from the immune system (e.g. Lens protein, myelin basic protein).

➢ **Molecular mimicry** by invading pathogens, in which immune responses are directed at antigenic determinants on pathogens that share identical or similar epitopes with normal host tissue. This phenomenon occurs in **rheumatic fever following *Streptococcus pyogenes* infection**, in which heart damage is thought to arise from an immune response directed against streptococcal antigens shared with heart muscle.

Autoimmunity:

- The suggested viral etiology of autoimmune diseases has been ascribed to immune responses (both cell-mediated and humoral) directed against virus epitopes that mimic sequestered self antigens.

- Inappropriate expression of class II MHC molecules on the membranes of cells that normally do not express class II MHC (e.g. islet beta cells). Increased expression of MHC II may increase presentation of self peptides to T helper cells, which in turn induce CTL, T_{DTH}, and B-lymphocyte cells that react against self antigens.

Examples :-

- Rheumatoid arthritis
- Systemic lupus erythematosus
- Multiple sclerosis
- insulin-dependent diabetes mellitus (T1DM).

Immunodeficiency Diseases

- **Congenital**

➢ X-linked agammaglobulinemia

➢ Di George's syndrome

➢ SCID due to ADA deficiency → Infusion of the purified enzyme (**pegademase,** from bovine sources) and transfer of ADA gene-modified lymphocytes have both been used successfully to treat this disease.

- **Extrinsic**

➢HIV causing AIDS.

Immunosuppression

- **Glucocorticoids**

➢ Glucocorticoids lyse (in some species) and induce the redistribution of lymphocytes, causing a rapid, transient decrease in peripheral blood lymphocyte counts.

➢ Glucocorticoid-receptor complexes increase IkB expression, thereby curtailing activation of NF-kB, which increases apoptosis of activated cells.

➢ key proinflammatory cytokines such as IL-1 and IL-6 are downregulated.

➢ T cells are inhibited from making IL-2 and proliferating. The activation of cytotoxic T lymphocytes is inhibited.

➢ Neutrophils and monocytes display poor chemotaxis and decreased lysosomal enzyme release.

➢ Suppresses fresh immune response more effectively.

➢ Little effect on humoral immunity.

➢ Mainly suppresses CMI.

Therapeutic Uses

- They commonly are combined with other immunosuppressive agents to prevent and treat transplant rejection. High dose pulses of intravenous *methylprednisolone sodium succinate* are used to reverse acute transplant rejection and acute exacerbations of selected autoimmune disorders .
- Glucocorticoids also are efficacious for treatment of graft-*versus*-host disease in bone-marrow transplantation.
- Glucocorticoids are used routinely to treat autoimmune disorders such as rheumatoid and other arthritis's, systemic lupus erythematosus, systemic dermatomyositis, psoriasis and other skin conditions, asthma and other allergic disorders, inflammatory bowel disease, inflammatory ophthalmic diseases, autoimmune hematologic disorders, and acute exacerbations of multiple sclerosis .

Therapeutic Uses

- In addition, glucocorticoids limit allergic reactions that occur with other immunosuppressive agents and are used in transplant recipients to block first-dose cytokine storm caused by treatment with muromonab-CD3 and to a lesser extent thymoglobulin.

Toxicity

- Growth retardation in children
- Avascular necrosis of bone
- Osteopenia
- Increased risk of infection
- Poor wound healing
- Cataract
- Hyperglycemia
- Hypertension

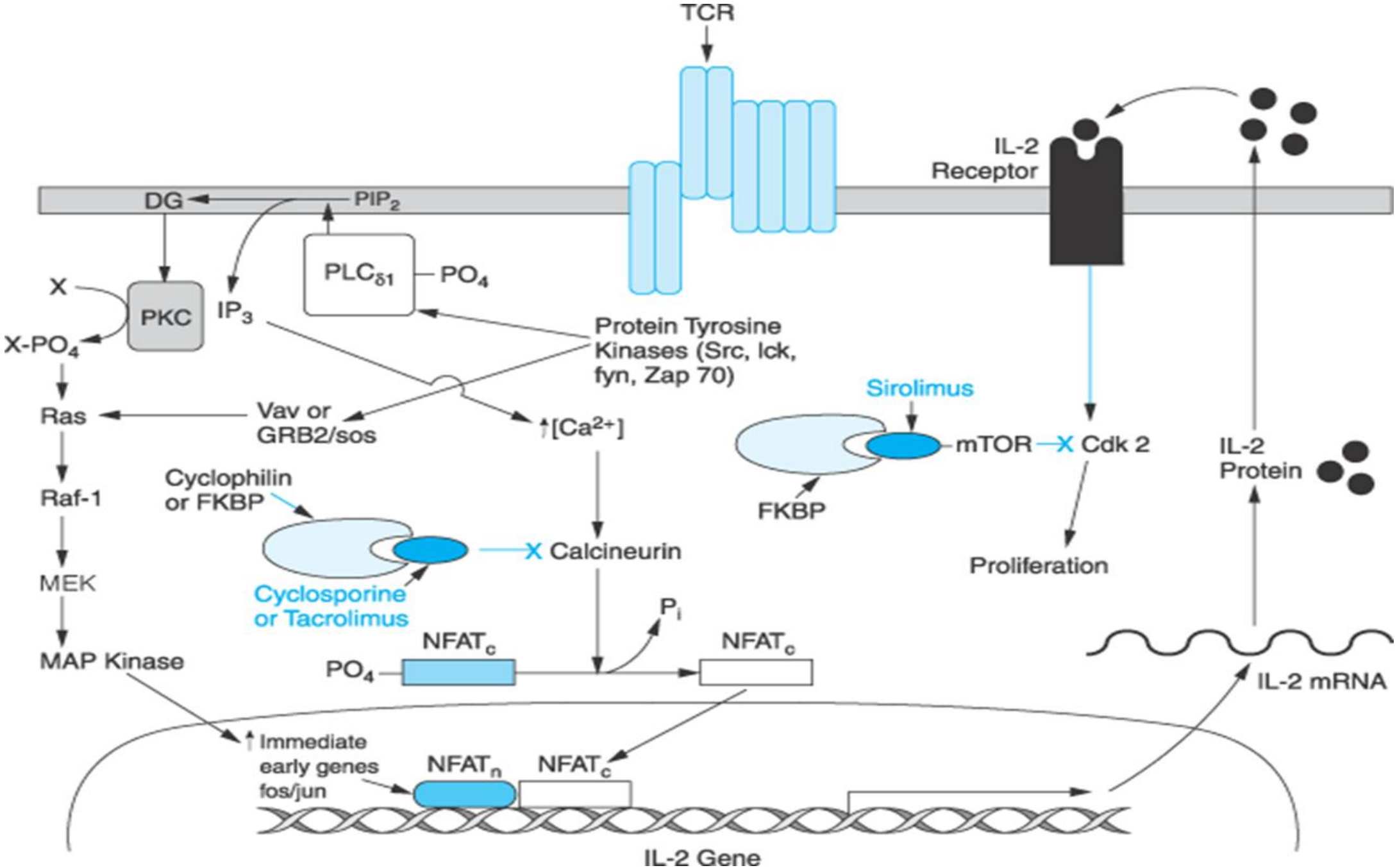
Calcineurin Inhibitors

Cyclosporine

- A fat soluble peptide antibiotic.
- Binds to cyclophilin and inhibits a cytoplasmic phosphatase calcineurin which is necessary for activation of a T cell specific transcription (NFAT) which causes synthesis of IL-2 by activated T cells.
- Metabolized by CYP3A enzymes.
- Adverse effects: Nephrotoxicity, hypertension, hyperlipidemia, hyperglycemia, liver dysfunction and hirsutism. Increased incidence of lymphoma and other cancers (Kaposi's sarcoma, skin cancer).
- Very low incidence of bone marrow toxicity.
- Used in renal, pancreatic and liver transplantation and also in RA, psoriasis, uveitis and asthma.

Tacrolimus (FK 506)

- This drug binds to FKBP-12.
- It is 10-100 times more potent than cyclosporine in inhibiting the immune response.
- Topical preparation available for use in atopic dermatitis and psoriasis.
- Nephrotoxicity, neurotoxicity (tremor, headache, motor disturbances, seizures), GI complaints, hypertension, hyperkalemia, hyperglycemia, and diabetes.
- Since tacrolimus is metabolized mainly by CYP3A, the potential interactions like with cyclosporine also apply for tacrolimus .
- Coadministration with cyclosporine results in additive or synergistic nephrotoxicity; therefore a delay of at least 24 hours is required when switching a patient from cyclosporine to tacrolimus.


TCR
IL-2 Receptor
DG
PIP2
PLCδ1
PO4
X
X-PO4
PKC
IP3
Protein Tyrosine Kinases (Src, lck, fyn, Zap 70)
Ras
Vav or GRB2/sos
↑[Ca2+]
Sirolimus
mTOR
X Cdk 2
FKBP
IL-2 Protein
Raf-1
Cyclophilin or FKBP
X Calcineurin
Proliferation
MEK
Cyclosporine or Tacrolimus
Pi
NFATc
PO4
NFATc
MAP Kinase
IL-2 mRNA
↑ Immediate early genes fos/jun
NFATn
NFATc
IL-2 Gene

Proliferation Signal Inhibitors

Sirolimus (rapamycin) and its derivative **Everolimus:**

- Binds to and inhibits a protein kinase, designated *mammalian target of rapamycin* (mTOR), which is a key enzyme in cell-cycle progression . Inhibition of mTOR blocks cell-cycle progression at the $G_1 \rightarrow S$ phase transition.
- In patients experiencing or at high risk for calcineurin inhibitor-associated nephrotoxicity, sirolimus has been used with glucocorticoids and mycophenolate mofetil to avoid permanent renal damage.
- Incorporated into stents to inhibit local cell proliferation and blood vessel occlusion.

Proliferation Signal Inhibitors

Sirolimus (rapamycin) and its derivative **Everolimus:**

- Since sirolimus is a substrate for CYP3A4 and is transported by P-glycoprotein.
- Everolimus (40-*0*-[2-hydroxy] ethyl-rapamycin) is closely related chemically and clinically to sirolimus but has distinct pharmacokinetics.
- The main difference is a shorter half-life and thus a shorter time to achieve steady-state concentrations of the drug.

Toxicity:

- Dose-dependent increase in serum cholesterol and triglycerides that may require treatment .
- Anemia, leukopenia, thrombocytopenia, hypokalemia or hyperkalemia, fever, and gastrointestinal effects.
- Delayed wound healing may occur.
- As with other immunosuppressive agents, there is an increased risk of neoplasms, especially lymphomas, and infections. Prophylaxis for *Pneumocystis carinii* pneumonia and cytomegalovirus is recommended

Mycophenolate Mofetil

- Inhibits inosine monophosphate dehydrogenase which is a key enzyme in guanine nucleotide synthesis.
- Used in steroid refractory graft versus host disease, RA, SLE.
- Its antiproliferative properties make it the first-line drug for preventing or reducing chronic allograft vasculopathy in cardiac transplant recipients.
- Toxicities includes gastrointestinal disturbances (nausea and vomiting, diarrhea, abdominal pain) headache, hypertension, and reversible myelosuppression (primarily neutropenia).

Thalidomide

- Thalidomide is a sedative drug that was withdrawn from the market in the 1960s.
- Nevertheless, it has significant immunomodulatory actions and is currently in active use or in clinical trials for over 40 different illnesses.
- Inhibits angiogenesis and has anti-inflammatory and immunomodulatory effects.
- It inhibits tumor necrosis factor-alpha (TNF-α), reduces phagocytosis by neutrophils, increases production of IL-10, alters adhesion molecule expression, and enhances cell-mediated immunity via interactions with T cells.

Thalidomide

Uses:

- Multiple myeloma
- It was used for many years in the treatment of some manifestations of leprosy and has been reintroduced in the USA for erythema nodosum lepro sum;
- It is also useful in management of the skin manifestations of lupus erythematosus.

Adverse effects:

- The most important toxicity is teratogenesis.
- Peripheral neuropathy, constipation, rash, fatigue, hypothyroidism, and increased risk of deep vein thrombosis.
- Thrombosis is quiet frequent, particularly in the hematologic malignancy population, so that most patients are placed on some type of anticoagulant when thalidomide treatment is initiated.

Summary

- Immunomodulation is a therapeutic approach in which we try to intervene in auto regulating processes of the defense system.

- Immunomodulators can act by two ways which are immunosuppression and immunostimulation.

THANKS