

Immunosuppression

Immunosuppression involves an act that reduces the activation or efficacy of the immune system.

Some portions of the immune system itself have immuno-suppressive effects on other parts of the immune system, and immunosuppression may occur as an adverse reaction to treatment of other conditions.

Immunosuppressant

An immunosuppressant is any agent that causes immunosuppression, including immunosuppressive drugs and some environmental toxins.

One of the primary uses of immunosuppressant drugs is to lower the body's ability to reject a transplanted organ, such as a liver, heart or kidney.

**What are they
Used for?**





Almost everyone who receives an organ transplant has to take immunosuppressant drugs.

If the new organ came from an identical twin, however, one may not have to take them.

When one gets an organ transplant, our body knows that the new organ is foreign.

This triggers a response by the body's immune system to attack it.



The body will attack the new organ and try to damage or destroy it.

The immunosuppressant drugs suppress the body's ability to do this.

The drugs allow the transplanted organ to remain healthy and free from damage.

The goal is to adjust these drugs to prevent rejection and to minimize any side effects of the drugs.

Classification

These drugs can be classified into 4 categories.

1. Selective inhibitors of cytokine production and function
2. Immunosuppressive antimetabolites
3. Antibodies
4. Adrenocorticoids

Selective inhibitor of cytokine production and function

- Cyclosporine
- Everolimus
- Sirolimus
- Tacrolimus



Cytokines are soluble, Antigen Non specific, signaling proteins that bind to cell surface receptors on a variety of cells.

The term cytokines includes the molecules known as interleukins (ILs), interferons (IFNs), tumor necrosis factors (TNFs), transforming growth factors and colony stimulating factors.

Cyclosporine

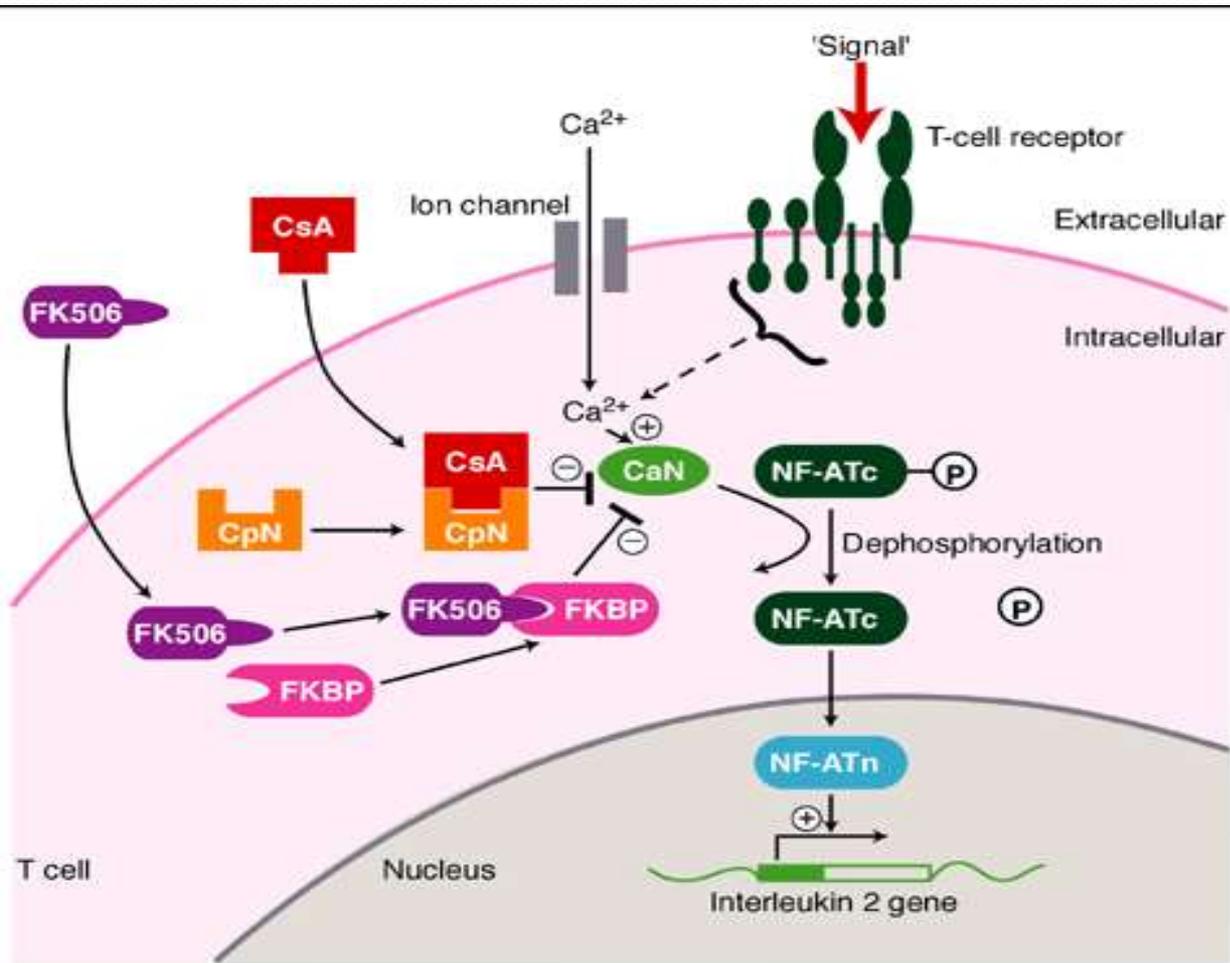
Mechanism of action:

Cyclosporine preferentially suppresses cell mediated immune reactions, whereas Humoral immunity is affected to a far lesser extent.

Cyclosporine blocks the transcription of cytokine genes in activated T cells.

After diffusing into the T cells, cyclosporine binds to a cyclophilin to form a complex that binds to calcineurin. The latter is responsible for dephosphorylating NFATc. Because the cyclosporine-calcineurin complex can't perform this reaction, NFATc can't enter the nucleus to promote the reactions that are required for the synthesis of a number of cytokines, including IL₂.

The end result is a decrease in IL-2, which is the primary chemical stimulus for increasing the no. of T-lymphocytes.



Mechanism of action of cyclosporine or tacrolimus (FK506)

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Tacrolimus

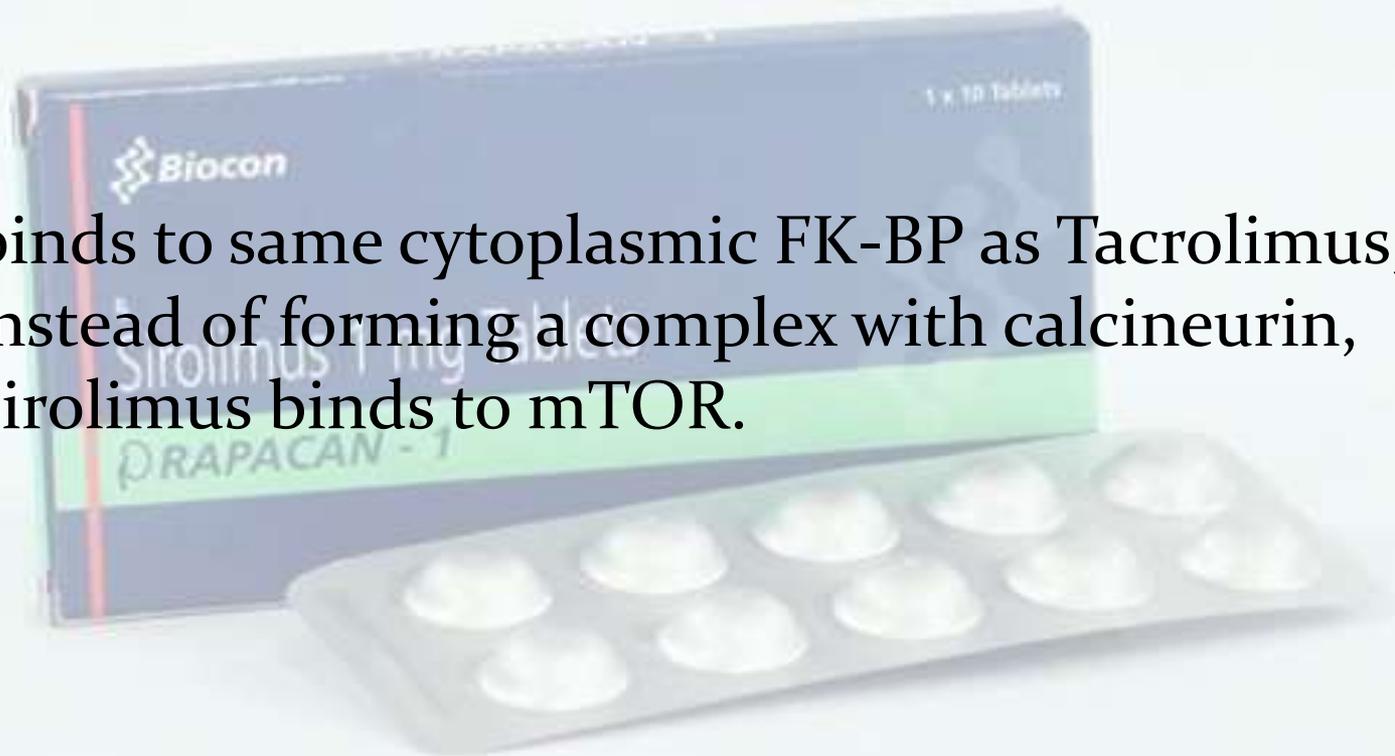
Mechanism of action

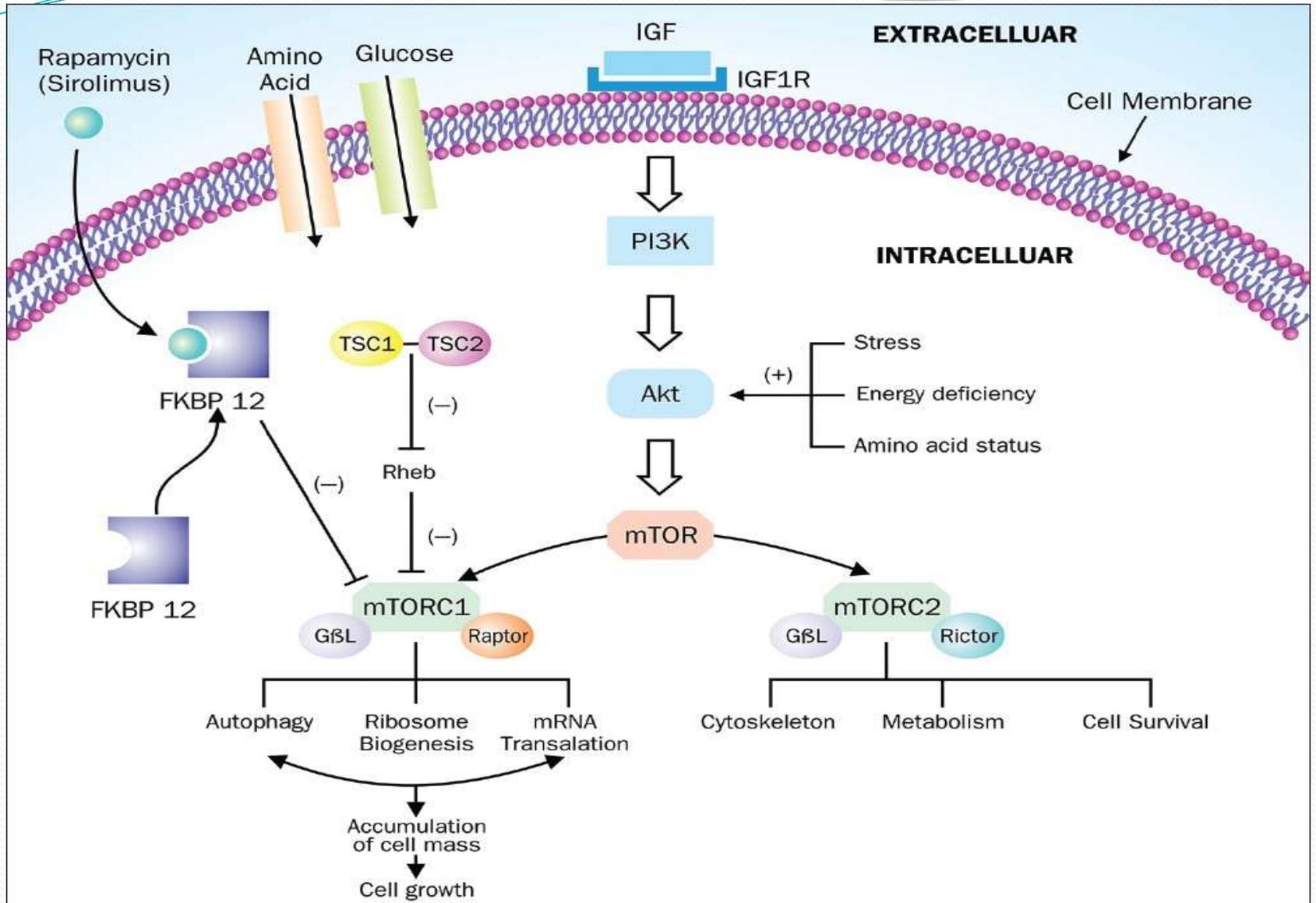
It exerts its immunosuppressive effects in the same manner as cyclosporine, except that it binds to a different immunophilin, FK-binding protein-12



Sirolimus

It binds to same cytoplasmic FK-BP as Tacrolimus, but instead of forming a complex with calcineurin, Sirolimus binds to mTOR.





Immunosuppressive antimetabolites

- Azathioprine
- Mycophenolate mofetil
- Mycophenolate sodium

These agents are generally used in combination with corticosteroids and calcineurin inhibitors, cyclosporine and Tacrolimus.

Azathioprine

An immunosuppressive antimetabolite pro-drug.

It interferes with the purine synthesis and is cytotoxic.

This drug is converted into 6-mercaptopurine and then to the corresponding nucleotide, thioinosinic acid that inhibit DNA synthesis.

Mycophenolate mofetil

Mechanism of action

It is converted into mycophenolic acid, which retains proliferation of both T and B lymphocytes and reduce the production of cytotoxic T cells by inhibiting inosine monophosphate dehydrogenase, an enzyme crucial for de novo purine biosynthesis in both T and B cells, so the drug has fairly selective action.



10 x 10 capsules



Antibodies

- Alemtuzumab
- Antithymocyte globulins
- Basiliximab
- Daclizumab
- Muromonab-CD₃

Alemtuzumab

It exerts its effects by causing profound depletion of T cells from the peripheral circulation.

Antithymocyte globulins

Thymocytes are developed in thymus and serve as precursors. The antibodies bind to the surface of circulating T lymphocytes, which then undergoes complement mediated destruction, Ab. Depending cytotoxicity, apoptosis and opsonization. The Ab. Bound cells are phagocytosed in the liver and spleen, resulting in lymphopenia and impaired T-cell responses.

IL-2 receptor antagonist

- Basiliximab
- Daclizumab

Mechanism of action

Both compounds are anti-CD-2 antibodies and bind to the α chain of the IL-2 receptor on activated T-cells. They thus interfere with the proliferation of these cells. Basiliximab is 10 fold more potent than Daclizumab as a blocker of IL-2 stimulated T-cell replication. Blockade of this receptor foils the ability of any antigenic stimulus to activate the T-cell response system.

Muromonab-CD3

Mechanism of action

Binding to CD3 protein results in a disruption of T-lymphocyte function, because access of antigen to the recognition site is blocked. Circulating T-cells are depleted, thereby decreasing their participation in the immune response. Because muromonab recognizes only one antigenic site, the immunosuppression is less broad than that seen with the polyclonal antibodies. T cells usually return to normal within 48 hours of discontinuation of therapy.

Corticosteroids

- Methylprednisolone
- Prednisolone
- Prednisone

Mechanism of action

The exact mechanism responsible for immunosuppressive action of corticosteroids is unclear.

The T-lymphocytes are effected mostly. The steroids are able to rapidly reduce lymphocyte populations by lysis or redistribution. On entering the cells, they bind to glucocorticoid receptor. The complex passes into the nucleus and regulates the translation of DNA.

Among the genes affected are those involved in inflammatory responses.