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Immunology

Doctor 2018 | Medicine | JU

Sheet ○ Slides

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This lecture will be a bit different from the previous ones. We'll be talking about immunopharmacology focusing on drugs that suppress the immune system.

These drugs mainly target **cytokines**. Remember that cytokines are soluble, antigen-nonspecific signaling proteins that bind to cell surface receptors on a variety of cells. Cytokines include the following:

- Interleukins (ILs)
- Interferons (IFNs)
- Tumor necrosis factors (TNFs)
- Transforming growth factors
- Colony-stimulating factors

❖ Immunosuppressive drugs/agents are clinically used for:

- Organ transplantation.
- Autoimmune Disorders. E.g. SLE, rheumatoid arthritis.
- Isoimmune Disease, e.g. hemolytic disease of newborn which results from blood group incompatibility between the mother and the newborn.
- *Prevention* of cell proliferation

e.g. 1) Coronary stents → use of drug-eluting-stent (a device that releases drug slowly) to prevent cell proliferation and blood clotting in certain vascular conditions.
2) Neovascular macular degeneration.

Immunosuppressive drugs include glucocorticoids, calcineurin Inhibitors, proliferation signal inhibitors, mycophenolate mofetil (an anti-metabolite), thalidomide, cytotoxic agents, immunosuppressive antibodies and monoclonal antibodies.

We'll start talking about glucocorticoids.

Glucocorticoids

Glucorticoids are endogenously produced steroids from the adrenal gland for different bodily functions. They can also be given as drugs in a variety of conditions. Glucorticoids have the followings properties:

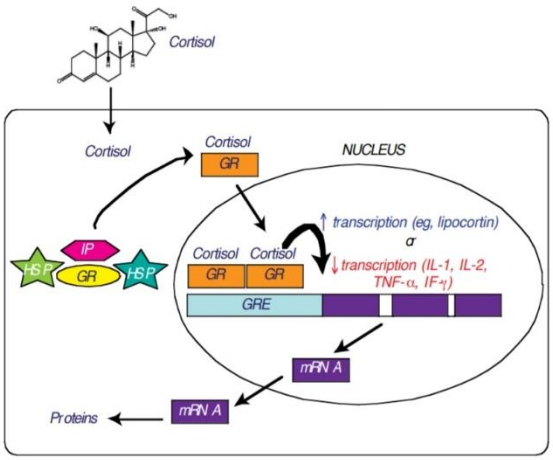
- ✓ First hormonal agents recognized as having lympholytic properties; they are able to cause lysis of lymphocytes. They're **cytotoxic** to certain subsets of T cells.
- ✓ They *increase* catabolic rate of immunoglobulins like IgG.
- ✓ Although the exact mechanism of their action hasn't been identified, it's known that they cause their *anti-inflammatory* and *anti-allergic* activities by 2 ways:
  A) Their action mainly suppresses the cell-mediated immunity by *inhibiting* genes that code for the cytokines, the most important of which is **IL-2** which is associated with proliferation and activation of T cells→ *Less cytokine production reduces T cell proliferation.*

  ⇒ Glucocorticoids also suppress the humoral immunity, causing B cells to express *smaller* amounts of **IL-2 and IL-2 receptors**, thus decreasing antibody responses. **Cellular immunity is more affected than humoral immunity.**

B) They *inhibit* phospholipase A2 thus inhibiting the production of arachidonic acid → inhibition of leukotriene and prostaglandin production → Anti-inflammatory effect.

➢ General mechanism of action

As you know, glucorticoids are **lipid soluble**. So, their target receptors are **intracellular receptors.** Let's take cortisol as an example. Cortisol enters the cell by diffusing through the plasma membrane → It then bind to its intracellular glucorticoid receptor (GR) ***activating*** it → upon activation, GR is translocated to the nucleus where it binds to certain DNA regions to *regulate* the expression of certain genes. It ***upregulates*** anti-inflammatory molecules like lipocortin and ***downregulates*** pro-inflammatory molecules like IL-1, IL-2, TNF-α, IF-γ.



GR, glucocorticoid receptor; HSP, heat shock protein; IP, immunophilin;GRE, glucocorticoid receptor

⇒ **Net effect: reduction of inflammation.**

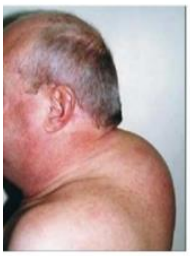
Now, what are the clinical uses of glucocorticoids?

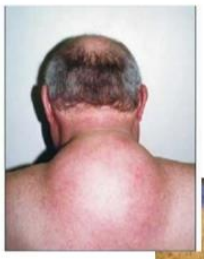
A) First-line immunosuppressive therapy for:
–Solid organ transplant
–Hematopoietic stem cell transplant recipients
–Graft-versus-host disease (GVHD).
B) Auto-immune diseases e.g. Idiopathic thrombocytopenic purpura and rheumatoid arthritis.
C) In some inflammatory conditions like bronchial asthma.
D) Premedication for agents (e.g. blood products, and drugs) known to cause undesirable immune responses, so we use glucocorticoids before the administration of these immunogenic drugs.

Just like any other drug glucocorticoids have side effects

1- Since glucocorticoids regulate metabolism in the body, they cause changes in the metabolic pathways e.g. they can cause **hyperglycemia** and **abnormal fat distribution** which has a characteristic appearance in patients who use these drugs **chronically**. Fat is mainly predisposed around the belly, dorsal neck area (buffalohump) and in the face (moonface). *Check the next page.*

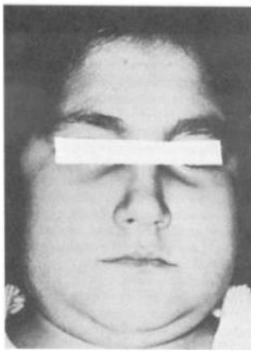
Buffalo Hump





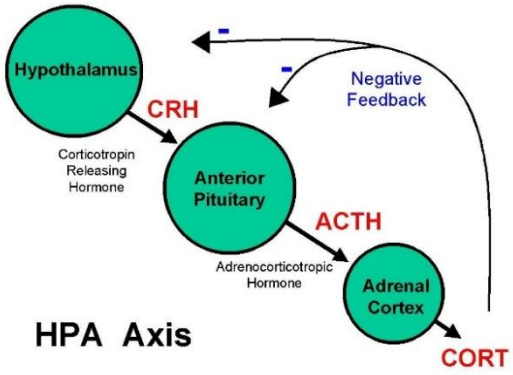
Predisposition of fat in the dorsal neck area

Moon Face



2- **Adrenal crisis.**

Glucocorticoids concentration must be maintained at *certain* levels in the body, and remember that they are produced from the adrenal gland which is under the regulation of the **hypothalamus** and the **pituitary gland**. Thus, an elevated concentration of glucocorticoids circulating in the body causes a **negative feedback** that affects the hypothalamus and the pituitary gland *stopping* the release of a hormone called **ACTH** which usually stimulates the production of glucocorticoids from the adrenal glands.



Now, if we start getting glucocorticoids from an **exogenous** source (*especially if chronically; more than 80mg for more than 2 weeks*) like cortisol, the body decreases the production of glucocorticoids. So, if the patient **abruptly** stops taking these drugs, and **low levels** are produced endogenously, the body goes into **adrenal crisis** since the amount of these hormones must be maintained at certain levels.

> To quit administration of glucocorticoids, the dose should be tapered gradually until it becomes zero, to make sure that the body resumes the synthesis of glucocorticoid sequentially.

3- **Immunodeficiency**. They are anti-inflammatory agents, thus making the patient more prone to infections.
4- **Growth failure** and delayed puberty, by affecting growth hormone release from adrenal gland.
5- **Excitatory effects** on central nervous system (euphoria, psychosis)
6- **Osteoporosis**, especially in older patients.
7- **Cataract**
8- **Gastric irritation** and ulceration.

Let's start talking about a second group of drugs.

Drugs affecting IL-2 levels

These drugs can be further divided into three main classes:

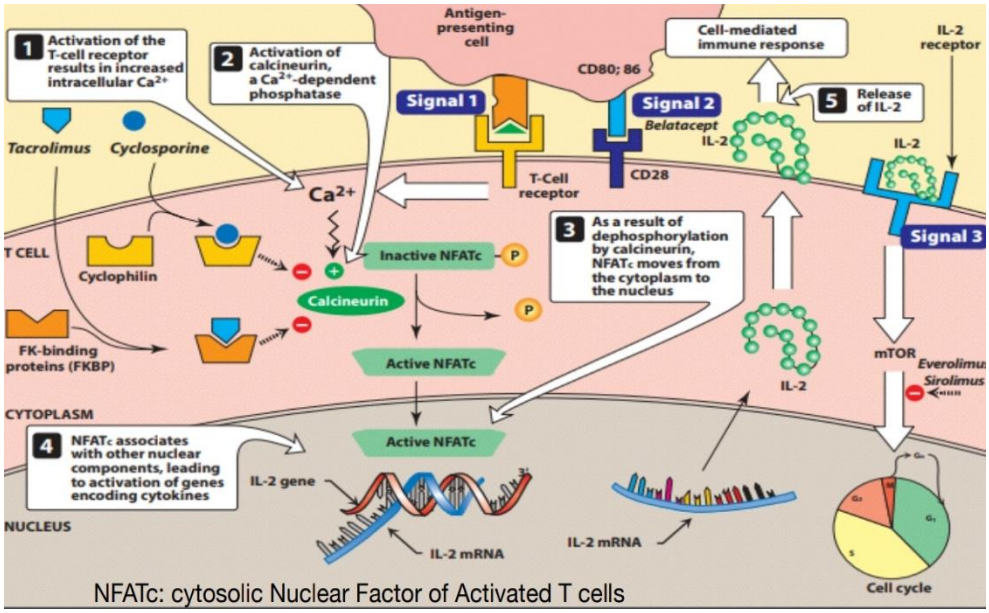
A. Calcineurin inhibitors (cyclosporine and tacrolimus)
B. Co-stimulation blockers (belatacept)
C. mTOR inhibitors (sirolimus and everolimus)

Why IL-2?
1- It activates NK cells, macrophages, and cytotoxic T-cells
2- It acts as a growth factor stimulating the proliferation of antigen-primed (helper) T-cells which causes increased production of more IL-2, IFN-γ, and TNF-α from different immune cells. Check the table to review the functions of some cytokines.

Cytokine	Actions
IL-1	• Enhances activity of NK cells • Attracts neutrophils and macrophages
IL-2	• Induces proliferation of antigen-primed T cells • Enhances activity of NK cells
IFN-γ	• Enhances activity of macrophages and NK cells • Increases expression of MHC molecules • Enhances production of IgG_{2a}
TNF-α	• Cytotoxic effect on tumor cells • Induces cytokine secretion in the inflammatory response

Before talking about these drugs, let's go over the ways of immune activation of T-cells. (three signal model)

Signal 1 constitutes of T-cell triggering at the CD3 receptor complex by an antigen on the surface of antigen-presenting cell (APC).
Signal 2 (costimulation) occurs when CD80 & CD86 on the surface of APCs engage with CD28 on T-cells. Both signals 1,2 activate several intracellular signal transduction pathways one of which is the **calcium-calcineurin pathway**: after interaction between the APC and the T-cell→ a cascade of events result in the *elevated* levels of **calcium**→ calcium causes *activation* of an enzyme called **calcineurin** which is a **Ca^{2+} dependent phosphatase** → upon its activation, calcineurin *removes* the phosphate group from a protein called **NFATc** *activating* it →

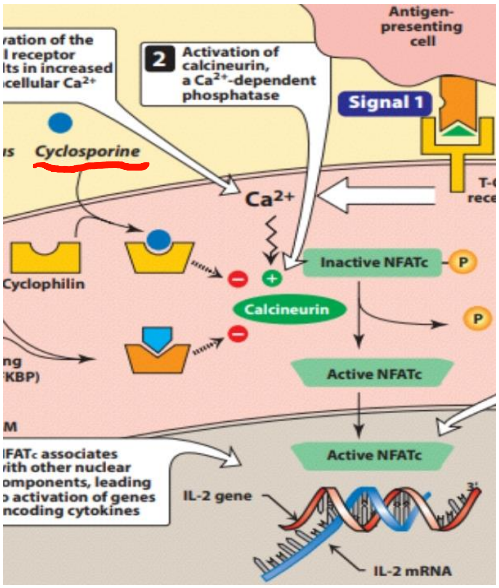


NFATc: cytosolic Nuclear Factor of Activated T cells

activated NFATc is translocated to the nucleus, it binds to DNA resulting in the expression of certain genes that produce cytokines, specifically IL-2 (also IL-15, CD154, CD25) which then will be secreted from the cell. → IL-2 then binds to its receptor (CD25) on the surface of other T-cells to activate **mTOR** (mammalian target of rapamycin), providing signal 3, the stimulus for T-cell proliferation.

If we interfere with any of the steps in the 3 signals using drugs, we can decrease the production of IL-2 and decrease T-cell proliferation. (Anti-inflammatory)

The first drug we'll be talking about is ***cyclosporine***



➢ Cyclosporine- Mechanism of action

It binds to a protein (immunophilin) called **cyclophilin** forming a complex (cyclosporine-cyclophilin) which *inhibits* **calcineurin** thus *inhibiting* **the activation of NFATc, IL-2 production & T-cell proliferation.**

⇒ It *suppresses* cell-mediated immune reactions, but humoral immunity is affected to a far **lesser** extent.
⇒ It is actually an antibiotic coming from a natural source.

➢ Therapeutic uses of Cyclosporine

A) To *prevent* rejection of kidney, liver, and cardiac allogeneic transplants
B) Combined in a **double-drug** or **triple-drug** regimen with
1.Corticosteroids 2. antimetabolite such as Mycophenolate mofetil.
C) Cyclosporine may also be used for **recalcitrant psoriasis.**

Recalcitrant: unresponsive to initial drug so⇒ use cyclosporine. Psoriasis: skin condition.

➢ Pharmacokinetics of Cyclosporine

-Cyclosporine can be given in two forms, **orally** and **IV infusion**
-Oral absorption vary between individuals, thanks to these two mechanisms that are do not occur in the same rate and degree in all people.
A) P-glycoprotein: pumps the drug out to the intestinal lumen, reducing absorption.

B) First-pass effect: our drugs get metabolized in the intestines by cytochrome P450 (CYP3A4)
So, we need to keep monitoring the drug's concentration in plasma.
-Excretion of the drug is primarily through the biliary route into the feces.

➢ Adverse effects of Cyclosporine

• **Nephrotoxicity**. (especially if it's given with other nephrotoxic drugs. E.g. Gentamicin)
• **Hypertension.** • **Hyperglycemia.** • **Liver dysfunction.** • **Hyperkalemia.**

- **Altered mental status, seizures.**
- **Hirsutism:** unwanted, male-pattern hair growth in women
- Gum hyperplasia (gingival hyperplasia). **If you patient is taking cyclosporine or nifedipine, keep in mind that this condition might be a side effect of drugs he's taking, not a dental problem.**

- **Lymphoma and other cancers** (Kaposi's sarcoma, skin cancer) due to induction of TGF-β.

We need to be aware of **drug combinations when looking at the previous list.*
Example: If a patient is on diuretics or other drugs that increase K^+ levels in the plasma, you can't give him cyclosporine simply because both of them cause hyperkalemia. Taking them together may pose a risk to the heart, as potassium level is essential for the cardiac muscle action.

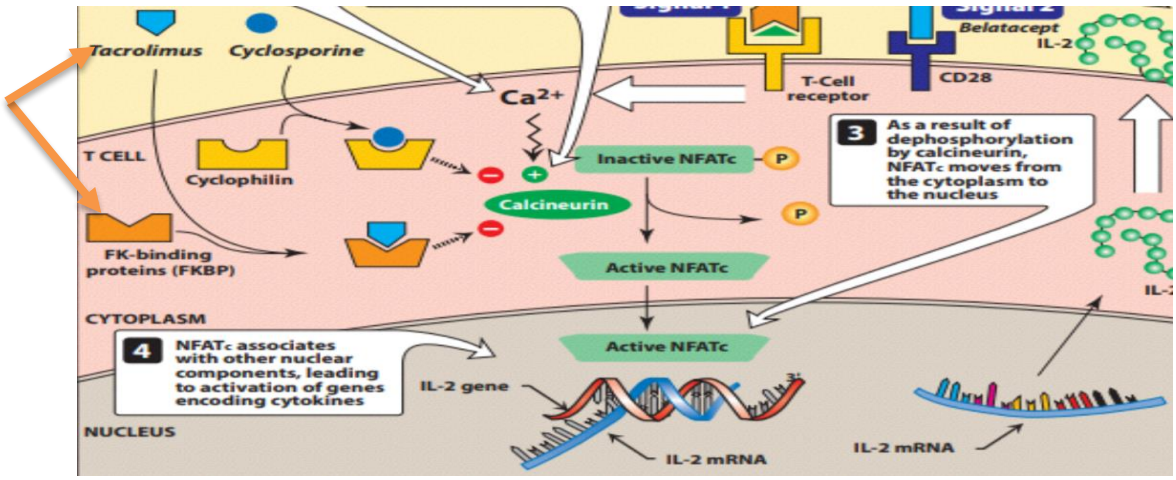
➢ Cyclosporin Monitoring Parameters

- **Cyclosporine trough levels.** • **Serum electrolytes.**
- **Renal function. Remember the nephrotoxicity**
- **Hepatic function. Remember the hepatotoxicity**
- **Blood pressure.**
- **Serum cholesterol. Note that this drug increases cholesterol level in the plasma**

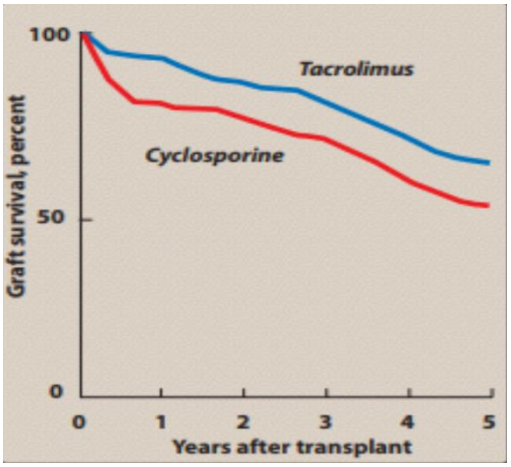
*Now we'll take about a second drug, which is **Tacrolimus***

➢ Tacrolimus- Mechanism of action

-Tacrolimus works by binding to an immunophilin called **FK- binding protein** and inhibiting calcineurin pathway that we've mentioned earlier. Calcineurin is inhibited → **NFATc** stays phosphorylated → It stays inactive → It won't reach the nucleus → IL-2 genes are not activated nor transcribed.



Why to use Tacrolimus instead of Cyclosporine?
-It is more potent than cyclosporine.
-It needs low doses of glucocorticoids to be used along with it, unlike cyclosporine.
-It decreases rejection of grafts, more than cyclosporine (has better five-year survival rate). Check the figure →



➢ Therapeutic Uses of Tacrolimus

• Preventing **liver and kidney rejections** (along with glucocorticoids).

• **Heart and pancreas transplants** and rescue therapy in patients after failure of standard rejection therapy.

• **Atopic dermatitis** unresponsive to conventional therapies.

➢ Pharmacokinetics of Tacrolimus

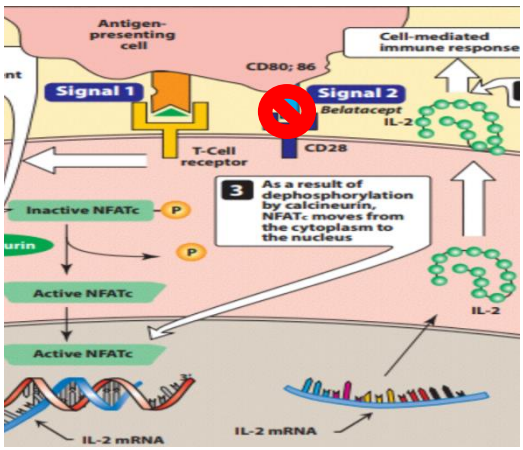
-It can be given orally or through IV, while the oral route being the preferable one.
-It is subject to P-glycoprotein and first pass metabolic effect. So, absorption is variable and **tailoring** the dose is needed.
-Absorption is decreased if the drug is taken with **high-fat** or **high carbohydrate** meals.
-The drug is excreted mainly through feces.

➢ Adverse effect of Tacrolimus

-It has similar adverse effects to that of cyclosporine, **nephrotoxicity and neurotoxicity** is more severe though.
-Development of posttransplant **insulin-dependent diabetes mellitus**, especially in black and Hispanic patients.
-It does not cause hirsutism or gingival hyperplasia but can cause **alopecia (hair loss)**.
-Its incidence of cardiovascular toxicities, such as hypertension and hyperlipidemia, is lower than that of cyclosporine.

Moving to our third drug today, which is called ***Belatacept.*** *This drug is a protein that was produced by recombinant DNA technology. And it is 2nd generation too! Sounds cool, right?*

➢ Belatacept- Mechanism of action



- Belatacept **blocks** **CD28**-mediated co-stimulation of T lymphocytes (signal 2) by binding to **CD80** and **CD86** on APCs. This prevents the downstream stimulatory signals which promote T-cell survival, proliferation, and IL-2 production.

➢ Therapeutic uses of Belatacept

• **Kidney transplantation** in combination with basiliximab, mycophenolate mofetil (will be discussed later), and corticosteroids.
• This drug can take the place of the calcineurin inhibitors to avoid the detrimental long-term cardiovascular, metabolic, and renal complications
• Note: **The first-generation** co-stimulation blocker **abatacept** is approved for **rheumatoid arthritis**.

➢ Pharmacokinetics of Belatacept

-It is taken in two rounds – steps.
-Initially, we give a **high dose on a frequent manner**. Later, the dose is **decreased and administered less frequently** (e.g. once in a month) and this is called maintenance phase. **Notice that the second step (monthly dosing) is so beneficial with patients having low compliance.**
- Belatacept clearance is not affected by **age, sex, race, renal, or hepatic function** because it is a protein after all.

➢ Adverse effects of Belatacept

-Belatacept increases the risk of **post-transplant lymphoproliferative disorder (PTLD)**, particularly of the central nervous system. **It is contraindicated in those patients who have never been exposed to the Epstein-Barr virus (EBV)**, a common cause of PTLD. **Remember: being exposed to this virus gives you some sort of immunity.**
Other common adverse effects include: **Anemia, Diarrhea, Urinary tract infection, Edema.**

Good Luck!!