Immuno pharmacology

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🧠 Immune system has an important function of protecting our body, however, sometimes it goes in another way of working and become harmful to the host, this harm come from what we called exaggeration in immune system response.

=e.g: Sepsis; when bacteria reaches the blood, our immune system response become enormous.

=e.g: COVID-19; some people their immune system response in a proper way they recover 😀 بينشفوا, however, those who response in an exaggerated way they develop cytokine storm and this make a state of instability in the body so our body attack lung cells and that what kill them.

**another example is autoimmune diseases, such as: Rheumatoid arthritis (immune cells attack joints), Systemic Lupus Erythematosus, Psoriasis الصدفية, Inflammatory bowel disease (IBD),, all these disease result from exaggeration in immune response.

🧠The role of pharmacology in this field is to increase or decrease the immune response using drugs, so we should be precise to avoid any problem.

Where

When we use immuno pharmacology?

- **Agents that modulate the immune system play an important role in:**

1. **Preventing the rejection of organ or tissue grafts**
   (as the rejection made by T cells toward transplanted organ, we need to inhibit it)

2. **In the treatment of certain diseases that arise from dysregulation of the immune response.**
   - **Autoimmune diseases.**
   - **Immunodeficiency diseases.**

In covid 19 , exaggeration in the immune response causes manifestations and may cause death

Solid Organ and Bone Marrow transplantation

- Four types of rejection can occur in a solid organ transplant recipient: **hyper-acute, accelerated, acute,** and **chronic.**

  During the surgery — Within days — Within 3 months — Within years

  - Transplant of organ introduces foreign tissue to the body
  - The body's immune system sees this foreign tissue, thinks it's bad and start producing lymphokines including IL-2

    IL-2 cause migration of the immune cells

  - The lymphokines then activates the immune system even further, leading to a nasty cycle of foreign tissue destruction rejection

-IL-2 do migration of immune system cells, and when activated cells arrive, they activate more immune cells, this lead to exaggeration which attack the transplanted organ and destroy it; so we need to inhibit the immune system.

- important note: there is NOT two patients have the same MHC (or the same antigens) even if they are identical twins, identical twins DNA differ in the area which is responsible of immune genes (so there's rejection of transplantation between them).

The drugs we use to inhibit the immune system are called Transplant Rejection agents.

- transplant rejection agents are narrow spectrum agents so we need special way to deal with them.

Narrow spectrum agents ➡️ special way to deal with them

Transplant Rejection agents complexity

- Many problems exist in currently approved regimens:

1. **Treatments are often very complex.** Many drugs
2. **low patient compliance.** Patients neglect taking medication
3. **Therapeutic margins can be very narrow.** Accurate doses to avoid toxicity
4. **Pharmacokinetic interaction potential is high and causes problems.** May contraindicate with other drugs

Remember : P450 metabolism

Unfortunately, these agents also have the potential to cause disease and to increase the risk of infection and malignancies.

Note : even identical twins have different MHC

=when we transplant any organ (heart, kidney, lung...etc) we need to do all possible ways to inhibit immune rejection, this mean that we need to control all ways that activate the immune system, so we do combination of drugs with different mechanisms of action and different toxicity BUT as we say these drugs are used for years maybe 4 or 5 with average of 3 years, and have narrow therapeutic window so the patient must take them in time to avoid over toxicity (on the kidney) or under activity (means there is rejection).

*Moreover, these drugs are metabolised by cytochrome P450, so it may interact with other drugs if taken together which cause increase or decrease of their concentration in the blood.

you may notice that the use of these drugs for years make the patient immunocompromised which make him susceptible to infections so we should isolate him, another thing that he could develop cancer.

We should avoid all ways of rejection by combination of drugs that have different mechanisms & different toxicity

Groups

نوتس عالسريع :

- احنا هون عم بنقلل مناعة الجسم لمدة ٣ سنين بالمتوسط ، فالجسم رح يصير اكتر قابلية للinfections و رح تزيد احتمالية الcancers 😶
- لازم نكون جدا دقيقين باختيار الdoses ، لانه لو زاد رح يسبب toxicity و لو قل رح يسبب rejection و ما رح نستفيد من الدوا ☠️

- **Glucocorticoids**
- **Calcineurin inhibitors**
  - **Ciclosporin A**
  - **Tacrolimus**
- **IL-2 receptor ‘mabs’**

Monoclonal antibodies

  - **Basiliximab**
  - **Daclizumab**

Selective drugs , bind in specific location in the body

- **Anti-metabolites**
  - **Azathioprine**
  - **Mycophenolates**
  - **Leflunomide**
- **m-TOR inhibitors**
  - **Sirolimus**

TOR : a protein has a role in cell cycle ▶️ so we need to inhibit it to stop the T cells proliferation (immune system cells)

The Drugs That We Use:

-Glucocorticoids (or glococorticosteroid) which is the cortisone.

- Calcineurin inhibitors such as: Cyclosporin A & Tacrolimus.

-Anti-metabolites such as: Azathioprine, Mycophenolates &Leflunomide: we talk about them in cancer lectures specially 5-florouracil when we talk about colon cancer, we said that it enters the DNA and inhibit transcription because it produces false nucleotide.

-IL-2 receptor 'mabs' they block IL-2 reseptor, such as: Basiliximab & Daclizumab: these new drugs we call them Biologics, which means that its designed to bind to specific locations within the body and not affect all the body.

-m-TOR inhibitors (m-TOR is a protein responsible of cell cycle) such as: Sirolimus, so we stop immune cell proliferation between G1 and S phase by inhibiting m-TOR.

Used for asthma patients (magical drugs)

Glucocorticoids

- Glucocorticoids suppress the cell-mediated immunity. inhibiting genes that code for the cytokines, the most important of which is IL-2. + IL -1

- Smaller cytokine production reduces the T cell proliferation.

- Glucocorticoids also suppress the humoral immunity, causing B cells to express smaller amounts of IL-2 and IL-2 receptors.
  remember that IL-1 is important in activation and migration of T-cells

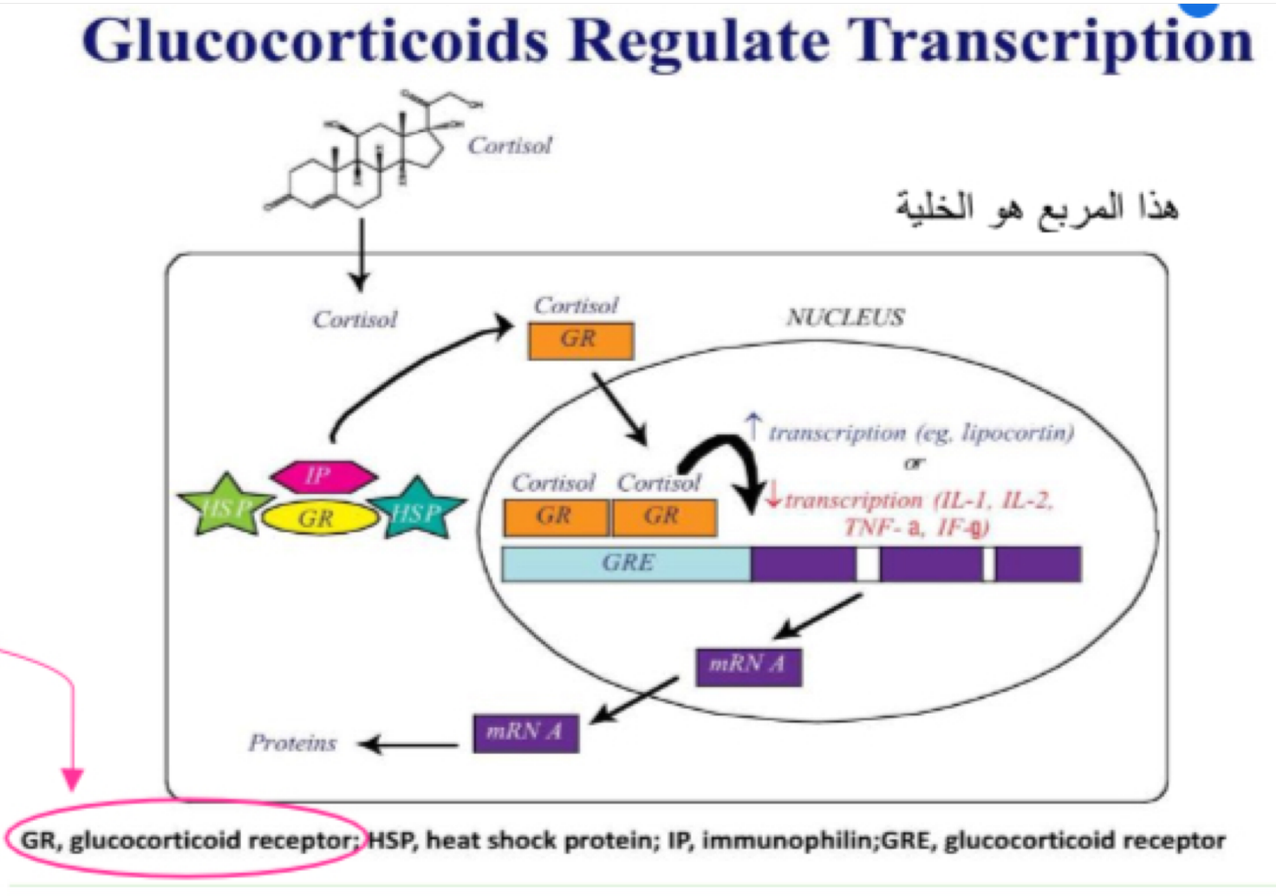
- Cellular immunity is more affected than humoral immunity.
  because smaller doses will affect cellular immunity.

- **Anti-inflammatory effects** + Immunosuppressive effect

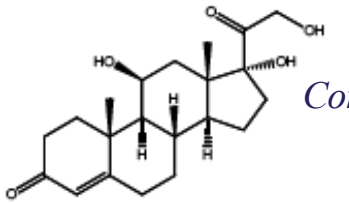
Glucocorticoids are also anti-inflammatory drugs (they are the strongest anti-inflammatory drugs), so we will use it in lots of cases (its magical drug).

= in treatment of any inflammation we start by giving glucocorticoids, e.g: asthma patient: they have inflammation in trachea and bronchi, so البخاخ we use this drug with other drugs as a mixture in the Symbicort this Symbicort has: long acting β2 agonist (LABA) + glucocorticosteroid

look at the picture... Cortisol (which is found in our bodies) cross the cell membrane, then it binds to its receptor inside the cell,, then this complex (GR) enter the nucleus, then it bind to glucocorticosteroid receptor element (GRE) which found in the promoter region of many many genes (nearly quarter of the genes),,it induce some of them and inhibit the other; inhibit transcription of (IL-1, IL-2,TNF- a, IFN- g) which are responsible of T cell activation so it inhibit cellular immunity which is responsible of rejection, & increase transcription of (lipocortin) which has anti-inflammatory effect (by this glucocorticoids has anti-inflammatory effect).



Glucocorticoids Regulate Transcription



Cortisol

Cross the cell membrane

Cell membrane

Cortisol

Cortisol

GR

NUCLEUS

Anti inflammatory effect

Bind to its receptor and enter the nucleus

↑ transcription (eg, lipocortin)

or

↓transcription (IL-1, IL-2, TNF- a, IF-g)

Immunosuppressive effect

IP

HSP

GR

HSP

Cortisol Cortisol

GR GR

GRE

In promoter region of many genes

mRN A

mRN A

Proteins

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

Solid organs : liver ,kidney , heart , and lung

hematopoietic stem cell transplantation: bone marrow transplantation

Clinically

- Glucocorticoids are first-line immunosuppressive therapy for both solid organ and hematopoietic stem cell transplant recipients and graft-versus-host disease (GVHD).

يعني انا لما اعمل زراعة لنخاع العظم ، رح يصنع خلايا مناعية جوا الجسم المستقبل (يعني الاشي المزروع عم بهاجم الجسم😂)

Without reason

Red spots on the skin because internal bleeding

idiopathic thrombocytopenic purpura and rheumatoid arthritis.

immune disorder in which the blood doesn't clot normally ، cause excessive bruising and bleeding due to low level of platelets

autoimmune disorder that primarily affects joints.

- Glucocorticoids modulate allergic reactions and are useful in the treatment of diseases like asthma or as premedication for other agents (eg, blood products) that might cause undesirable immune responses

Like anaphylaxis

When I give the patient a dye for the purpose of an examination in the hospital and I want to avoid the allergy that can happen

★ Side Effects of Glucocorticosteroids:

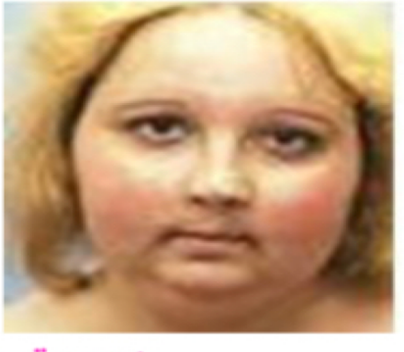
*before we transplant the organ we give the patient high dose of methylprednisolone 500 mg intravenously (IV and sometimes IM) to shut the immune system down, after transplantation we give the patient 20 mg daily for 6 months and we start to reduce the dose for another 6 months.

⇨ methylprednisolone is a synthesised glucocorticoid ⇦

1} Immunodeficiency

2} Adrenal glands will stop synthesise glucocorticoids because we give it externally so it will atrophies يضمر, to avoid this we start lowering the dose after 6 months.

3} Hyperglycemia because it increases the gluconeogenesis,, and Fat redistribution around the face and the neck (moon face and buffalo hump), because genes that are responsible for fat distribution are changed by using this drug.



4} Growth failure, delayed puberty.

5} Excitatory effect on central nervous system (euphoria زهزهة, psychosis):it enters the brain because its lipophilic.

6} Osteoporosis هشاشة عظام : because its reduces calcium deposition and increase the activity of osteoclast over the osteoblast if it used for more than 6 months so we use it just for 6 months. الدكتور ركز عالمدة كثير

7} Cataracts: increase the ocular presser إعتام عدسة العين

8} Gastric ulcers: (prevent with drugs that reduce the acidity such as: omeprazole, misoprostol) الأدوية هذول مش حفظ

9} hypertension.

🌀 so this drug affects all the body because it affect the gene expression of more than 20% of our genes. رغم كل هالمصايب مجبورين نعطيه لانو فش غيره

Change 25% of expressed genes in the body

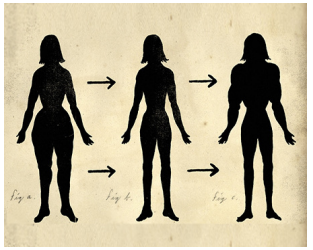
High doses (IV or IM) 500 mg before transplantation
Then 20 mg daily doses for 6 months
{Tipparing}

Side effect

Fat redistribution

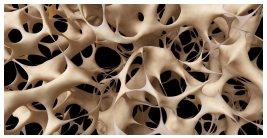
Moon face : flushed and round face

BFR syndrome

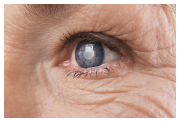


- **Immunodeficiency**
- adrenal glands
- gloconeogenisis Hyperglycemia Fat redistribution
- growth failure, delayed puberty.
- excitatory effect on central nervous system (euphoria, psychosis) depression

It's Lipophilic so can cross BBB and cause CNS diseases

- Osteoporosis 

Bones become brittle and fragile from loss of tissue

- Cataracts 

Lead to increase in the ocular pressure

- Gastric ulcers (prevent with omeprazole, misoprostol)
- Hypertension

Calcineurin Inhibitors
Cyclosporine & Tacrolimus

1. human organ transplantation,

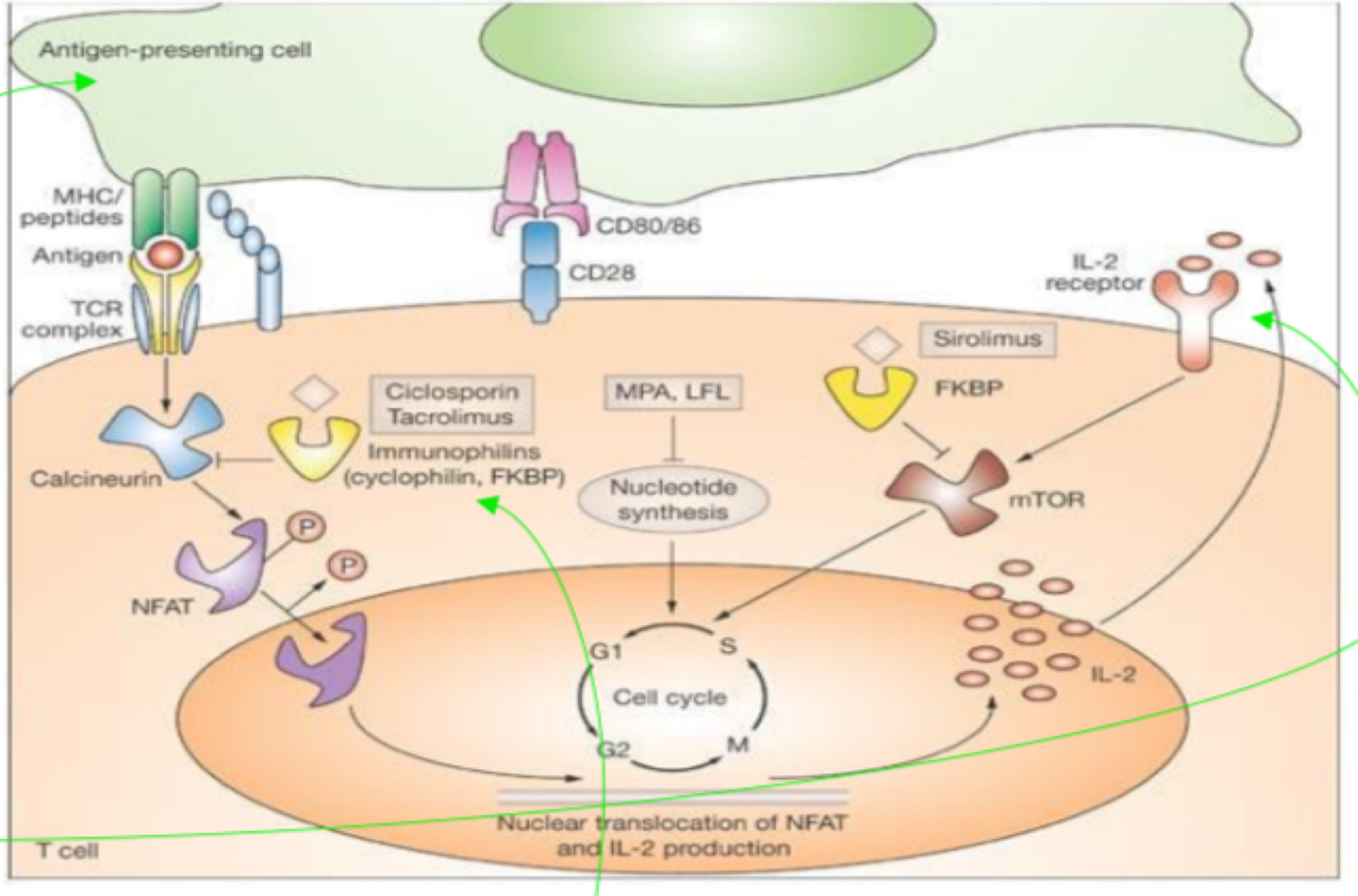
2. graft-versus-host disease after hematopoietic stem cell transplantation,

3. selected autoimmune disorders.

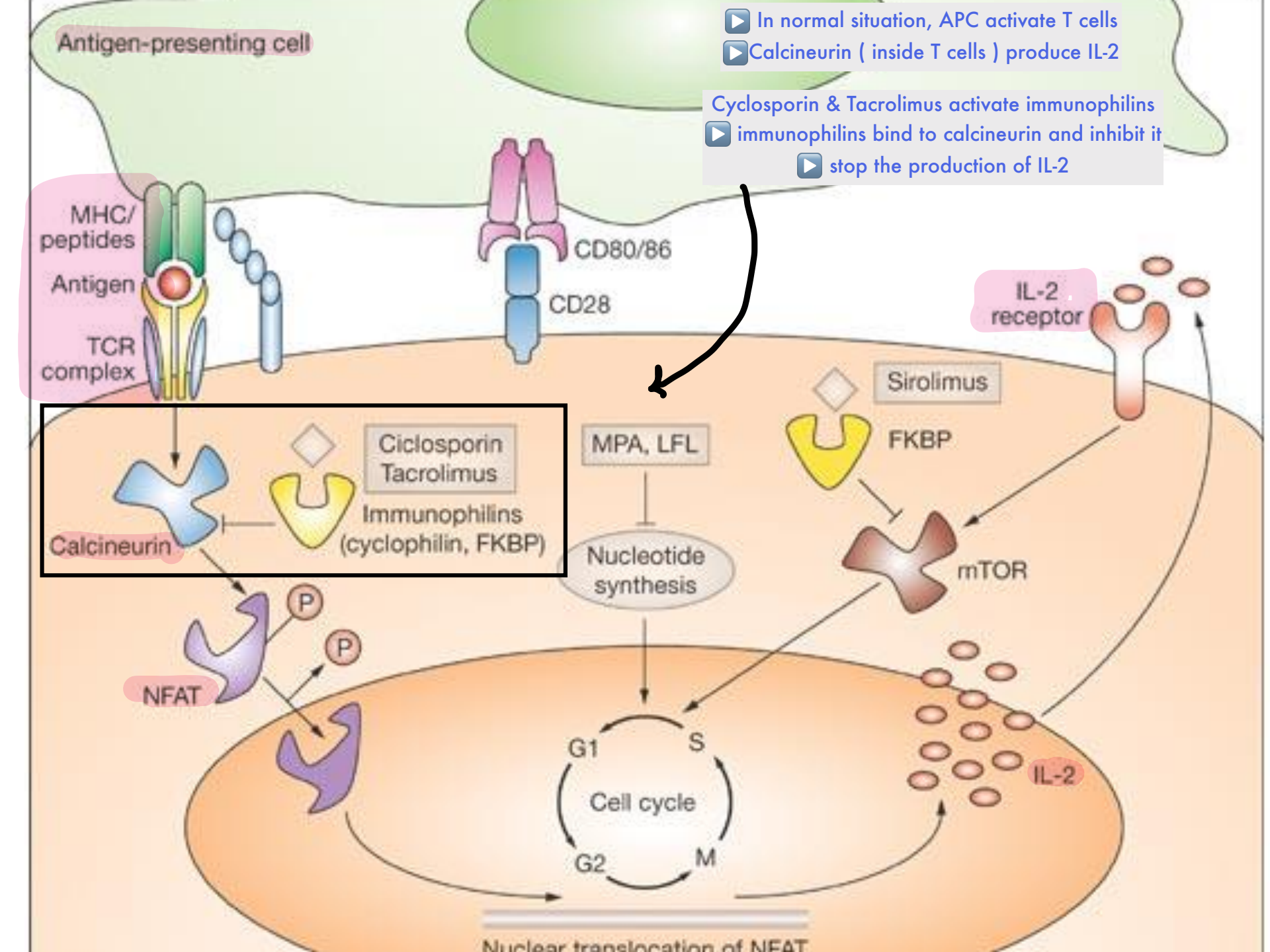
Both Inhibit the cytoplasmic phosphatase, calcineurin, which is necessary for the activation of a T-cell-specific transcription factor. This transcription factor, NF-AT, is involved in the synthesis of interleukins (eg, IL-2) by activated T cells.

So these drugs will affect indirectly the gene expression so its effect is less than glucocorticoid (because it has direct effect).

Look at the figure -as we see APC will activate T- cell by MHC binding to TCR which activates calcineurin, calcineurin as a phosphatase it dephosphorylates NFAT which in turn inter the nucleus and increase the expression of IL-2, IL-2 exit the cell and bind to its receptor on the cell surface (autocrine) which increase the activation and migration of T-cells.



our drugs in the cell bind to immnuophilins which has 2 types (cyclophilin which bind cyclosporine, FKBP which bind tacrolimus), now immunophilin when activated it inhibits calcineurin which in turn inhibit IL-2 and T-cell activation.


In normal situation, APC activate T cells
Calcineurin (inside T cells) produce IL-2
Cyclosporin & Tacrolimus activate immunophilins
immunophilins bind to calcineurin and inhibit it
stop the production of IL-2
Antigen-presenting cell
MHC/ peptides
Antigen
TCR complex
CD80/86
CD28
IL-2 receptor
Sirolimus
FKBP
Ciclosporin
Tacrolimus
Immunophilins (cyclophilin, FKBP)
Calcineurin
MPA, LFL
Nucleotide synthesis
mTOR
P
P
NFAT
G1
S
Cell cycle
G2
M
IL-2
Nuclear translocation of NFAT

A4 ▶ SNPs ▶ polymorphism ▶ slow , fast , intermediate metabolisers

Complexity

3A4 + 3A5

- metabolized by the P450 3A enzyme system in the liver with resultant multiple drug interactions.

IMPORTANT: CYP 3A4 and CYP 3A5 are polymorphic (has SNP single nucleotide polymorphism) which means that everyone has different activity of them, some patient are poor metabolisers and some are intermediate metabolisers and some are fast metabolisers and some are ultra-rapid-metabolisers,, so depending on the phenotype we determine the concentration in the patient's blood.

- Narrow therapeutic window ↵ in kidney transplantation
  - Levels too high: toxicities (i.e. nephrotoxicity, mental confusion, hyperglycemia and hypertension)
  - Levels too low: transplant rejection.

- Increased incidence of lymphoma and other cancers (Kaposi's sarcoma, skin cancer) have been observed in transplant recipients receiving cyclosporine,

Target drug monitoring:

cyclosporine is one of the drugs that we monitor it, we must determine it's concentration in the blood, so we should monitor:

>Cyclosporine trough قاع levels: we need to determine the lowest concentration of the drug after the first dose and before we give him the second dose, to know how much of it still in the blood

>Serum electrolytes: to make sure that it doesn't cause kidney toxicity because it affects their concentration in the blood.

>Renal function (because it causes renal toxicity).

>Hepatic function: because it also affects the liver (hepatotoxicity).

>Blood pressure: because it increases the blood pressure.

>serum cholesterol: because it increases the lipid amount in the body.

CYCLOSPORINE

اتذكروا لما كنا نحسب T 1/2 كنا كل فترة معينة نرجع نضيف dose
الفكرة هون ، انه بنقيس كمية الدوا اللي ضلت قبل ما نضيف الدوز الجديد عشان نعرف كم اللي ضل بالزبط و ما نعطي زيادة

Measure conc in patient's blood

Monitoring Parameters:

- Cyclosporine trough levels. — To prevent drug - drug interaction
- Serum electrolytes.
- Renal function. → Kidney toxicity
- Hepatic function. — Liver toxicity
- Blood pressure.
- serum cholesterol.

CYCLOSPORINE

- Cyclosporine ophthalmic solution is now available for severe dry eye syndrome, as well as ocular graft-versus-host disease.

- In combination with methotrexate, cyclosporine is a standard prophylactic regimen to prevent graft-versus-host disease after allogeneic stem cell transplantation.

- Cyclosporine has also proved useful in a variety of autoimmune disorders, including rheumatoid arthritis, psoriasis, and asthma.

Tacrolimus

- Because of the effectiveness of systemic tacrolimus in some dermatologic diseases, a topical preparation is now available. Tacrolimus ointment is currently used in the therapy of atopic dermatitis and psoriasis.

🧠 the same thing as cyclosporine, but it has low toxicity on the kidney so nowadays we prefer to use it BUT remember we should do blood monitoring (remember, it has narrow therapeutic window).
= it can cause Diabetes mellitus.