Immunopharmacology (Part 1)

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Topics in this lecture

- 1- Where to use immunopharmacology?

1- Where to use immunopharmacology?

- Agents that modulate the immune system play an important role in:
  1) Preventing the rejection of organ or tissue grafts
  2) In the treatment of certain diseases that arise from dysregulation of the immune response, such as:
  - Autoimmune diseases.
  - Immunodeficiency diseases.
  - Allergic rhinitis
- We can say that we use immunopharmacology everywhere, as in almost all diseases there is an inflammation, and the responsible of inflammation is the immune system
- E.g. of famous drugs: cortisol, glucocorticoid

2- Introduction about rejection

- Four types of rejection can occur in a solid organ transplant recipient:
  a- **hyper-acute: immediate rejection of the transplanted organ**
  b- accelerated: rejection within hours
  c- acute: rejection within 1 week to 3 months
  d- chronic: rejection 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
- The lymphokines then activates the immune system even further, leading to a nasty cycle of foreign tissue destruction rejection

3- problems in rejection treatment

- Many problems exist in currently approved regimens:

1. **Treatments are often very complex.**
2. **low patient compliance.**
3. **Therapeutic margins can be very narrow.**
4. **Pharmacokinetic interaction potential is high and causes problems.**

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

4- Drugs we will study in these lectures

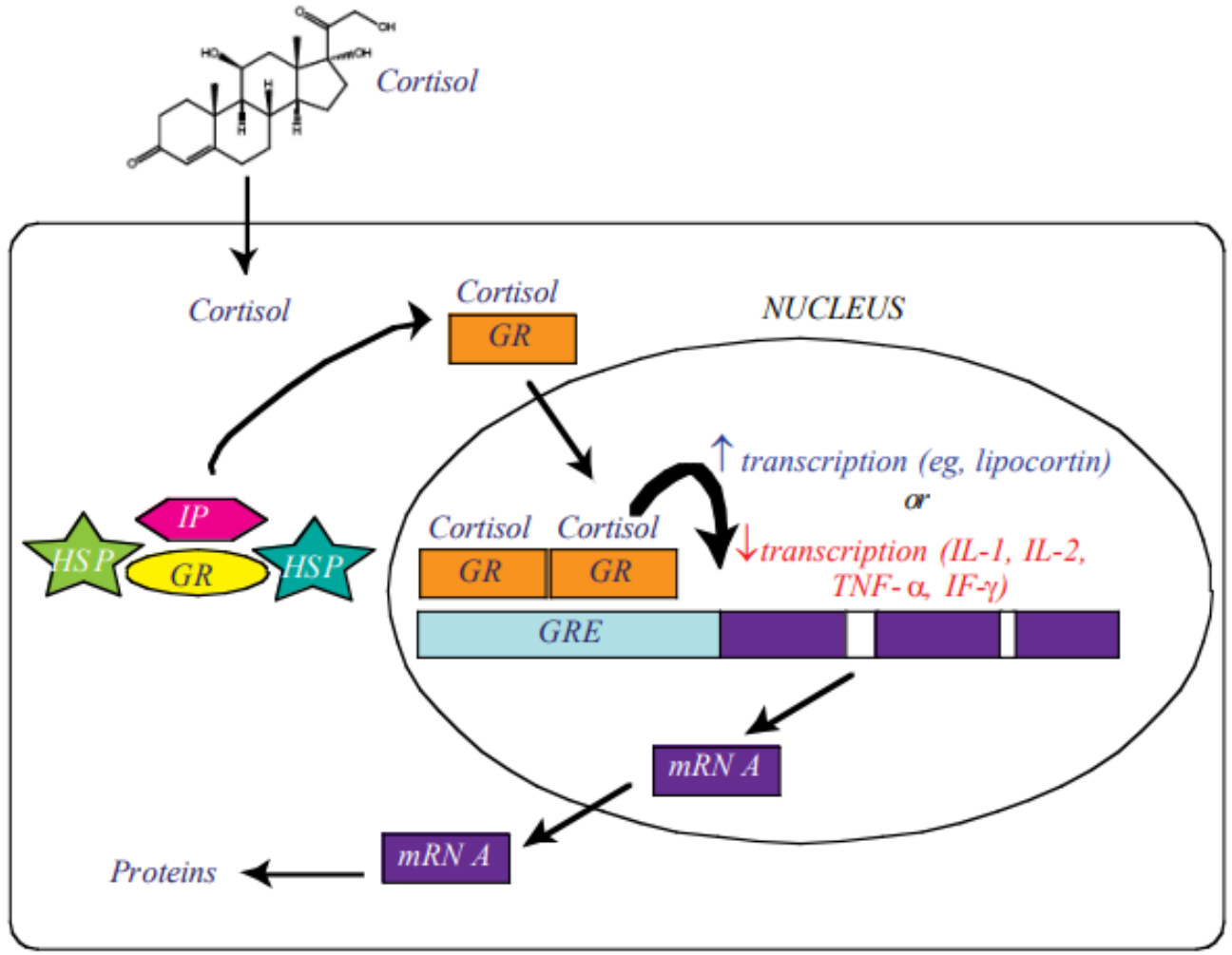
- Glucocorticoids
- Calcineurin inhibitors
  a- Ciclosporin A
  b- Tacrolimus
- Anti-metabolites
  a- Azathioprine
  b- Mycophenolates
  c- Leflunomide
- m-TOR inhibitors
  a- Sirolimus

5- Glucocorticoids

- Best drug used for therapy
- Most common example is cortisol
- Glucocorticoids suppress the cell-mediated immunity. inhibiting genes that code for the cytokines, the most important of which is IL-2.
- 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 (Sometimes IL-6)
- Cellular immunity is more affected than humoral immunity.
- **Anti-inflammatory effects**

5- Glucocorticoids

- Mechanism:
  1) Cortisol enters the cell and bind on it's receptor in the cytoplasm
  2) Then it binds with it's receptor on the glucocorticoid element (GRE) on the genome
  3) This enhance the transcription of lipocortin gene to produce lipocortin (Annexin 1), this structure inhibits Phospholipase 2 (Phospholipase 2 normally function in transcription of Cyclo-oxygenase to produce interleukins
  4) It inhibits also the direct transcription of IL-1, IL-6, TNF & IF-γ
- Note: before 24 hours of transplanting the organ we give the patient high dose of methylprednisolone 500 mg intravenously (IV and sometimes IM) to shut the immune system down



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

5- Glucocorticoids

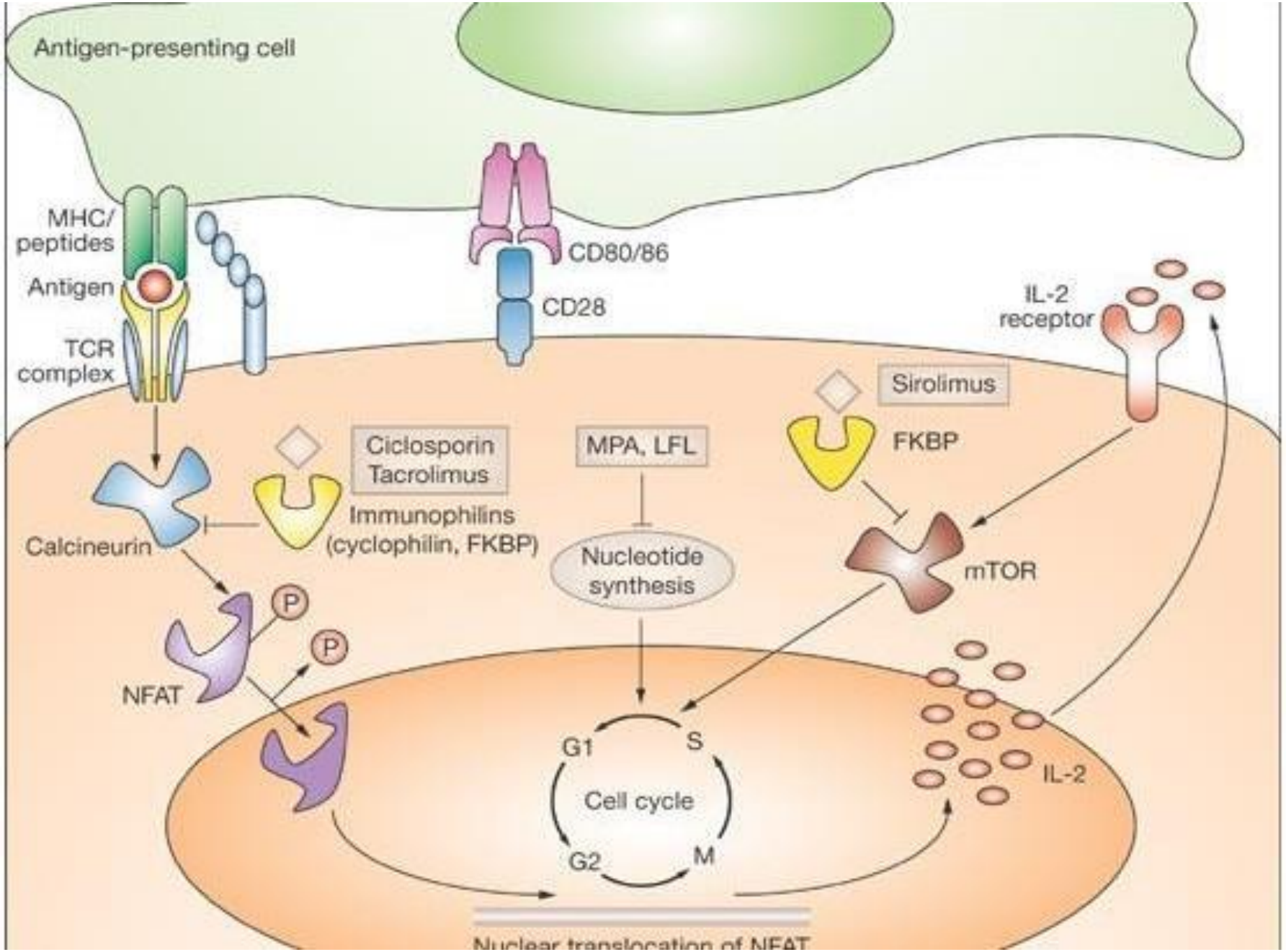
- Glucocorticoids are first-line immunosuppressive therapy for both solid organ and hematopoietic stem cell transplant recipients and graft-versus-host disease (GVHD).
- idiopathic thrombocytopenic purpura and rheumatoid arthritis.
- Glucocorticoids modulate allergic reactions and are useful in the treatment of diseases like asthma or as premedication for other agents (eg, blood products) that might cause undesirable immune responses.

5- Glucocorticoids

- Side effects of ORAL cortisol:
- 1} Immunodeficiency
- 2} Adrenal glands will stop synthesize glucocorticoids because we give it externally so it will atrophies after about 21 days of taking this drug, this is known as physiological effect
  Note: 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 ,psychosis):it enters the brain because its lipophilic.
- 6} Osteoporosis : 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.
- 7) Cataracts: increase the ocular presser
- 8) Gastric ulcers:(prevent with drugs that reduce the acidity such as:(misoprostol, omeprazole)

6- Calcineurin Inhibitors/ Cyclosporine & Tacrolimus

- Uses of calcineurin inhibitors:
  1) human organ transplantation
  2) graft-versus-host disease after hematopoietic transplantation
  3) selected autoimmune disorders. (E.g. asthma, RA, SLE)
- 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.


Antigen-presenting cell
MHC/
peptides
Antigen
TCR
complex
CD80/86
CD28
IL-2
receptor
Sirolimus
FKBP
Ciclosporin
Tacrolimus
Immunophilins
(cyclophilin, FKBP)
MPA, LFL
Calcineurin
Nucleotide
synthesis
mTOR
P
P
NFAT
G1
S
Cell cycle
G2
M
IL-2
Nuclear translocation of NFAT

6- Calcineurin Inhibitors/ Cyclosporine & Tacrolimus

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

  -Levels too high: toxicities (i.e. nephrotoxicity, mental confusion, hyperglycemia and hypertension)

  - Levels too low: transplant rejection.

  →Note: As it has low therapeutic window and metabolized by P450, we need to know the therapeutic window of each patient as the activity of P450 differs among people
- Increased incidence of lymphoma and other cancers (Kaposi's sarcoma, skin cancer) have been observed in transplant recipients receiving cyclosporine,

6- Calcineurin Inhibitors/ Cyclosporine & Tacrolimus

- Things we need to monitor in this drug:
- Drug trough levels: Not to get out of therapeutic window
- Serum electrolytes.
- Renal function.
- Hepatic function.
- Blood pressure.
- serum cholesterol

6- Calcineurin Inhibitors/ Cyclosporine & Tacrolimus

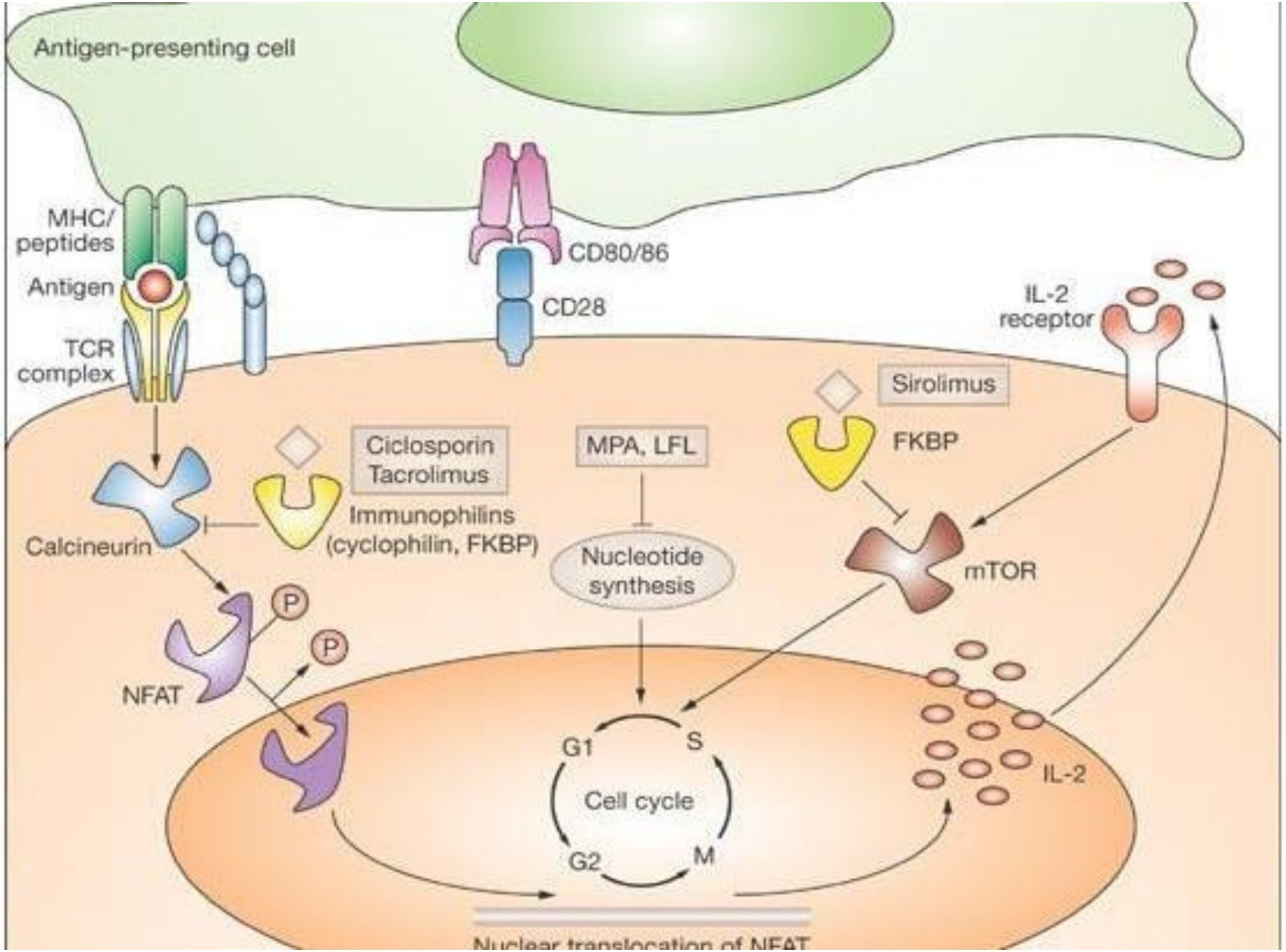
- Cyclosporine ophthalmic solution is now available for severe dry eye syndrome, as well as ocular graft-versus-host disease.
- In combination with methotrexate, cyclosporine is a standard prophylactic regimen to prevent graft-versus-host disease after allogeneic stem cell transplantation.
- Cyclosporine has also proved useful in a variety of autoimmune disorders, including rheumatoid arthritis, psoriasis, and asthma.

6- Calcineurin Inhibitors/ Cyclosporine & Tacrolimus

- Tacrolimus is the same 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 as it's worse in hyperglycemia
- It's more expensive

7- Sirolimus (RAPAMUNE)

- Inhibits immune cell growth through inhibiting the kinase activity of mammalian target of rapamycin (mTOR) and decreasing IL-2 activities.
- Narrow therapeutic window
  - Levels too high: toxicities (i.e. mental confusion, nephrotoxicity)
  - Levels too low: transplant rejection


Antigen-presenting cell
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TCR
complex
CD80/86
CD28
IL-2
receptor
Sirolimus
FKBP
Ciclosporin
Tacrolimus
Immunophilins
(cyclophilin, FKBP)
MPA, LFL
Calcineurin
Nucleotide
synthesis
mTOR
P
P
NFAT
G1
S
Cell cycle
G2
M
IL-2
Nuclear translocation of NFAT

8- Anti-metabolites

- Inhibiting proliferation of all replicative cells by inhibiting DNA synthesis, so They affect the proliferation of both T cells and B cells.
- These drugs are used in treating cancer, In immunotherapy, they are used in smaller doses than in the treatment of malignant diseases.
- Side effects: GI symptoms, bone marrow suppression and immunodeficiency

9- Conclusion

- We use a regimen of drugs when transplanting:
  Glucocorticoid (500 ml IV before the surgery and 20 ml daily after the surgery for 6 months) + Calcineurin inhibitors + anti-metabolites (Azathioprine) or m-TOR inhibitors (We prefer Anti-metabolites unless If there is diarrhea)
- The probability of rejection with this regimen is about 50%!