Immunopharmacology

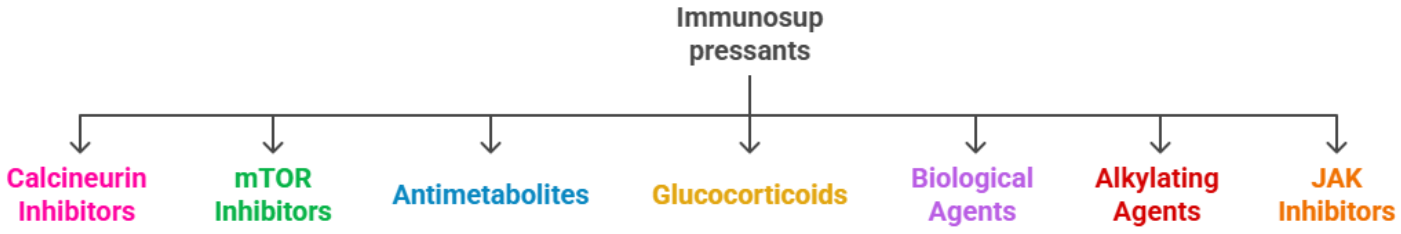
Pharmacology of Immunosuppressants

Introduction

- **Immunosuppressants** are a class of drugs that reduce or inhibit the strength of the body's immune response.
- These drugs are primarily used to:
  - Prevent organ transplant rejection
  - Treat autoimmune diseases
  - Manage hypersensitivity conditions
- The immune system is a double-edged sword: while it protects the host from infections, an overactive or misdirected immune response can result in tissue damage, autoimmune diseases, or rejection of transplanted organs.
- Immunosuppressants are therefore critical in modulating immune function under specific clinical circumstances.
- These agents can act at various stages of the immune response, including:
  - T cell activation and proliferation
  - Cytokine production
  - Antibody formation
  - Lymphocyte trafficking and survival

Classification of Immunosuppressants

Immunosuppressants can be classified into several categories based on their mechanism and origin:



1. **Calcineurin Inhibitors**
   - Cyclosporine
   - Tacrolimus
2. **mTOR Inhibitors**
   - Sirolimus (Rapamycin)
   - Everolimus
3. **Antimetabolites (Cytotoxic Agents)**

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- Azathioprine
- Mycophenolate mofetil
- Methotrexate

4. **Glucocorticoids**
   - Prednisone
   - Methylprednisolone
5. **Biological Agents (Monoclonal antibodies and fusion proteins)**
   - Muromonab-CD3 (OKT3)
   - Basiliximab, Daclizumab (anti-IL-2R antibodies)
   - Rituximab (anti-CD20)
   - Alemtuzumab (anti-CD52)
   - Belatacept (CTLA4-Ig fusion protein)
6. **Alkylating Agents**
   - Cyclophosphamide
   - Chlorambucil
7. **Janus Kinase (JAK) Inhibitors**
   - Tofacitinib
   - Baricitinib

Mechanism of Action

Each class of immunosuppressant has a distinct mechanism of action:

1. **Calcineurin Inhibitors**
   - Inhibit calcineurin, a calcium-dependent phosphatase required for activation of the transcription factor NFAT.
   - NFAT is essential for the transcription of IL-2, a key cytokine in T cell proliferation.
   - Thus, these drugs prevent T cell activation.
   - Cyclosporine binds to cyclophilin, while tacrolimus binds to FKBP-12; both complexes inhibit calcineurin.
2. **mTOR Inhibitors**
   - Bind to FKBP-12 and inhibit mTOR (mechanistic Target of Rapamycin), a serine/threonine kinase essential for cell cycle progression.
   - They inhibit IL-2 driven T-cell proliferation downstream of IL-2 receptor activation.
3. **Antimetabolites**

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- Inhibit DNA synthesis, selectively affecting proliferating lymphocytes.
- Azathioprine is a prodrug converted to 6-mercaptopurine, which inhibits purine synthesis.
- Mycophenolate mofetil inhibits inosine monophosphate dehydrogenase (IMPDH), which is crucial for de novo guanosine nucleotide synthesis, specifically in B and T lymphocytes.
- Methotrexate inhibits dihydrofolate reductase, preventing thymidine synthesis.

4. Glucocorticoids

- Inhibit multiple inflammatory genes by binding to the **glucocorticoid receptor**, suppressing **NF-κB and AP-1**.
- Decrease cytokine production, adhesion molecule expression, and lymphocyte proliferation.
- Cause **lymphocyte apoptosis**, especially of T cells.

5. Biological Agents

- Monoclonal antibodies or fusion proteins that target surface markers or cytokine receptors.
- Examples:
  - **Muromonab-CD3**: targets CD3 on T cells, causing depletion.
  - **Basiliximab**: blocks IL-2 receptor (CD25) on activated T cells.
  - **Rituximab**: depletes B cells by targeting CD20.
  - **Belatacept**: inhibits co-stimulatory signals by binding CD80/86.

6. Alkylating Agents

- Form cross-links in DNA, leading to apoptosis of rapidly dividing immune cells.

7. JAK Inhibitors

- Inhibit the **JAK-STAT** signaling pathway, reducing the transcription of pro-inflammatory cytokines.

Pharmacokinetics

The pharmacokinetics varies widely between classes:

Cyclosporine:

- Oral bioavailability: variable (30–70%)
- Metabolized by CYP3A4 in the liver
- Half-life: 6–20 hours
- Excreted via bile

Tacrolimus:

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- Oral bioavailability: 20–25%
- Highly protein-bound
- Metabolized by CYP3A4
- Half-life: ~12 hours

Sirolimus:

- Long half-life (~60 hours)
- Metabolized by CYP3A4
- Poor oral bioavailability (~15%)

Mycophenolate mofetil:

- Prodrug, converted to mycophenolic acid
- High oral bioavailability
- Glucuronidated in the liver
- Excreted in urine

Azathioprine:

- Prodrug of 6-mercaptopurine
- Metabolized by xanthine oxidase and thiopurine methyltransferase (TPMT)

Glucocorticoids:

- Well absorbed orally
- Metabolized by liver enzymes
- Excreted in urine

Biological agents:

- Administered parenterally
- Long half-lives due to protein structure
- Slow onset, prolonged action

Pharmacodynamics

- Onset of action varies from hours (glucocorticoids) to days or weeks (biologics).
- The degree of immune suppression depends on drug, dose, and patient factors.
- Drugs like cyclosporine and tacrolimus cause dose-dependent suppression of T-cell activity.
- Monoclonal antibodies often result in profound and prolonged suppression.

Adverse Effects

General adverse effects of immunosuppressants include:

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- Increased risk of **infections**
- **Malignancies**, especially lymphomas and skin cancers
- **Organ toxicity** (e.g., nephrotoxicity, hepatotoxicity)
- Hypertension
- Dyslipidemia
- Bone marrow suppression

Specific Adverse Effects:

Drug/Class	Adverse Effects
Cyclosporine	Nephrotoxicity, hypertension, hirsutism, gingival hyperplasia
Tacrolimus	Nephrotoxicity, neurotoxicity, diabetes mellitus
Sirolimus	Hyperlipidemia, delayed wound healing, thrombocytopenia
Azathioprine	Bone marrow suppression, hepatotoxicity, pancreatitis
Mycophenolate mofetil	GI upset, teratogenicity, bone marrow suppression
Glucocorticoids	Osteoporosis, hyperglycemia, Cushingoid features, psychosis
Rituximab	Infusion reactions, reactivation of hepatitis B

Contraindications

- Immunosuppressants are contraindicated or used with caution in:
  - Active infections
  - **Uncontrolled hypertension or diabetes** (especially with steroids and CNIs)
  - **Pregnancy** (especially mycophenolate, methotrexate)
  - **Severe hepatic or renal dysfunction** (depends on agent)
  - **Live vaccines** (contraindicated during immunosuppressive therapy)

Therapeutic Uses

Condition	Immunosuppressants Used
Organ transplantation (kidney, liver, heart)	Cyclosporine, Tacrolimus, Mycophenolate, Glucocorticoids
Rheumatoid arthritis	Methotrexate, Leflunomide, JAK inhibitors, Rituximab

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