

IMMUNOSUPPRESSIVES

Muhammad Al-Shorbagy, PhD
Pharmacology & Toxicology
Faculty of Pharmacy, Cairo University
mshorbagydr@staff.cu.edu.eg

Introduction

- Introduction of foreign antigen (**usually proteins, glycoproteins or high-molecular-weight carbohydrates**) into the body may provoke an immune reaction.

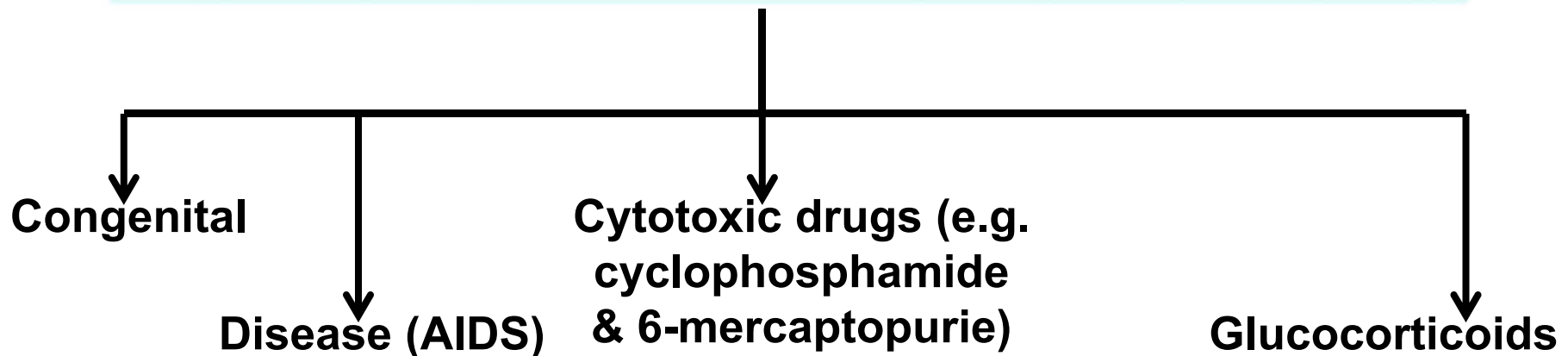
Types of immune responses:

- Humoral (via B-lymphocytes, plasma cells and antibody).
- Cellular (via T-lymphocytes).

Autoimmune diseases:

- If immune response becomes defective, disorganized or overactive → the body has the potential to stimulate its own immune system so that antibodies are produced against itself.

Deficiencies in immune system



These drugs used clinically as immunosuppressants when it is necessary to ↓ an inappropriate immune response.

Immunity & hypersensitivity

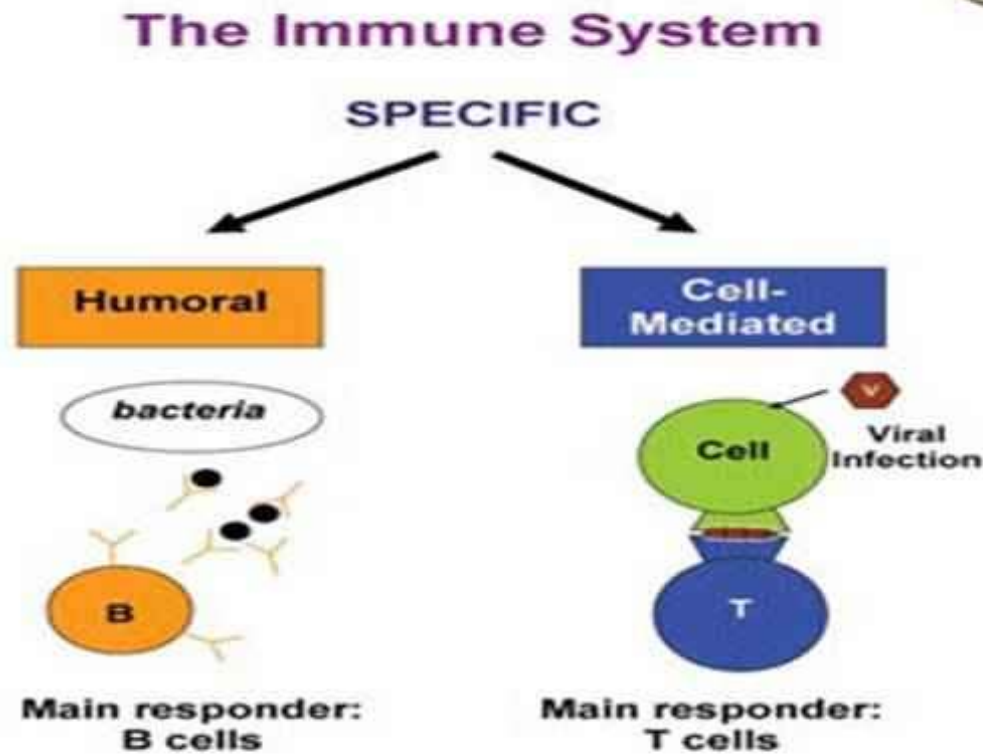
Humoral immunity:

The humoral response occurs in two stages:

1. **Primary reactions** – these occur with the first exposure to the antigen. There is a small and short-lived rise in antibody titre which consists largely of **IgM**.
2. **Secondary reactions** – these occur with subsequent exposure to the antigen. The rise in antibody titre is greater and persists for a long period. The antibody consists mainly of **IgG**.

Cellular immunity:

- Mediated by sensitized T lymphocytes which recognize and bind the antigen.



Active immunity:

- Consists of immunity that is developed either in response to **infection** or following **exposure to an attenuated strain of organism** to which the host produces protective antibodies.

Passive immunity:

- This is immunity that is transferred by the administration of preformed antibodies.

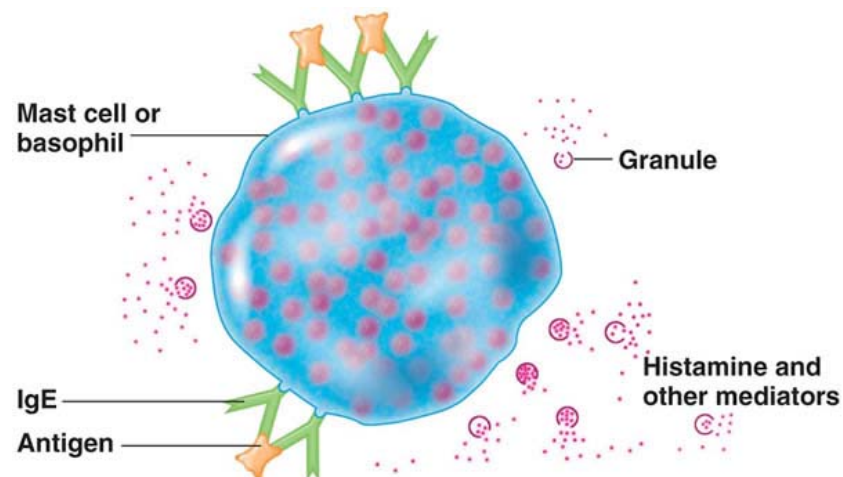
Hypersensitivity:

Occurs when the immune response to an antigen results in damage to the tissue.

Types:

1- Type-I Hypersensitivity:

- Combination of antigen with high affinity IgE antibody on the surface of tissue mast cells and/or blood basophils → releasing **histamine**, **prostaglandins**, etc
- This can cause anaphylaxis, bronchospasm, or urticaria.



(a) IgE antibodies, produced in response to an antigen, coat mast cells and basophils. When an antigen bridges the gap between two adjacent antibody molecules of the same specificity, the cell undergoes degranulation and releases histamine and other mediators.

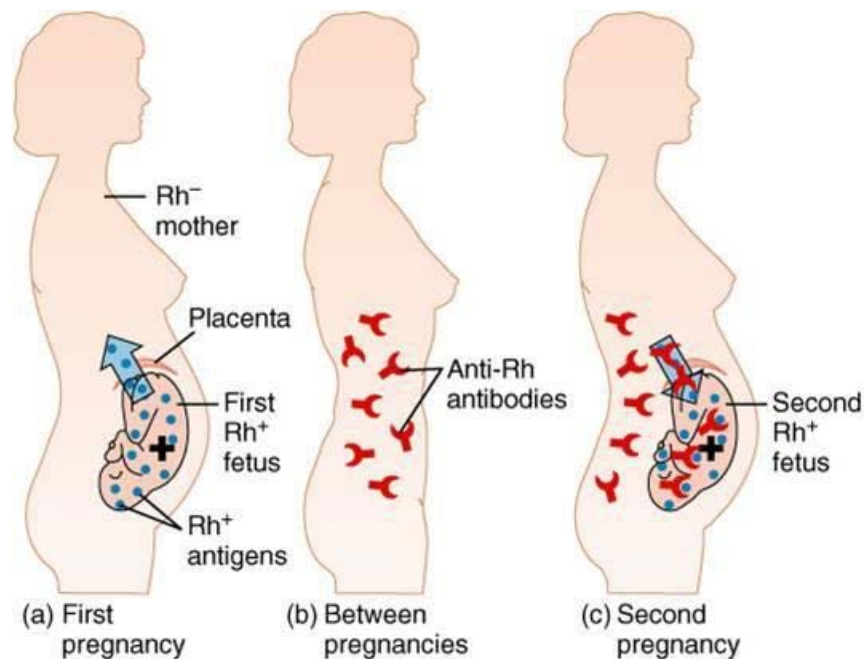
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2- Type-II hypersensitivity:

Example:

• Haemolytic disease of the newborn:

- When antibodies produced by a rhesus-negative (RH-ve) mother against the RH factor on the red cells of the fetus.
- The formed antibodies cross the placental barrier and cause haemolysis.
- Such reactions may be mediated by IgM or IgG antibodies.



3- Type-III hypersensitivity (immune complex mediated).

4- Type-IV (Delayed Or Cell-mediated Hypersensitivity).

Immunosuppressive agents

Immunosuppression should ideally be specific and not impairing immune responses indiscriminately.

General adverse effects

- **Increased susceptibility to infection:** e.g.: bacterial (**tuberculosis**), viral (**herpes**), & fungal (**candida**) may occur with increased frequency.
- **Sterility Azoospermia:** **in men** especially with alkylating agents. **In women,** hormone failure leading to amenorrhoea.
- **Teratogenicity:** avoid pregnancy while on these drugs.

Glucocorticoids

Mechanism of action

1. Bind to glucocorticoid receptors → ↓ production of inflammatory mediators as prostaglandins, leukotrienes, histamine, and bradykinin.
2. Decrease production of cytokines IL-1, IL-2, interferon, TNF (tumor necrosis factor).
3. Stabilize lysosomal membranes.
4. Inhibit antigen processing by macrophages.
5. Suppress T-cell helper function
6. Decrease T lymphocyte proliferation.

Glucocorticoids

Uses

1. Allergic rhinitis & atopic dermatitis (type-I reactions)
WHY?? Due to: non-specific anti-inflammatory effects, including vasoconstriction and decreased vascular permeability. It is also used in acute severe asthma, chronic asthma and anaphylaxis.
2. Type-II autoimmune diseases.
3. Type-III hypersensitivity.
4. Cell-mediated hypersensitivity (type IV) reactions. They are used to prevent acute graft rejection and improve severe contact dermatitis.

Calcineurin inhibitors: ciclosporin

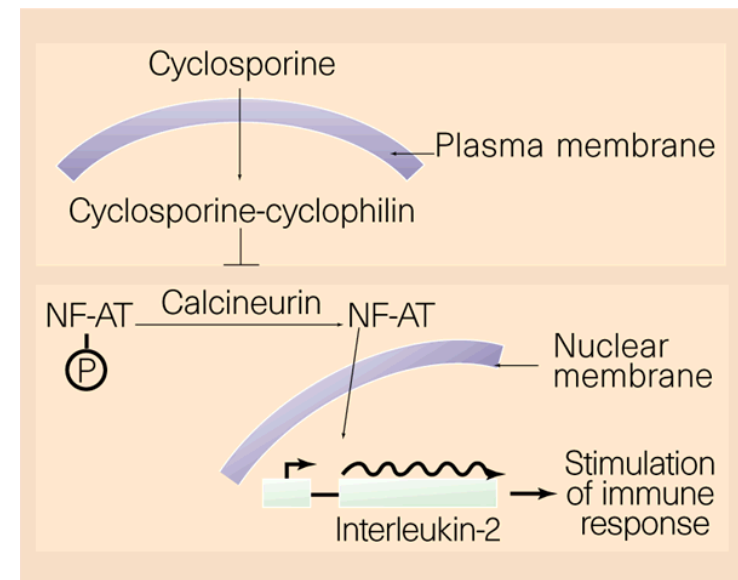
Uses

- Immunosuppression for solid-organ transplantation.

Mechanism of action

- Ciclosporin is a specific T-lymphocyte suppressor.
- It inhibits the production of interleukin-2 (IL-2) and other cytokines.

Ciclosporin binds to a cytosolic protein cyclophilin → This conjugate subsequently → reduces the formation of IL-2, other pro-inflammatory lymphokines and IL-2 receptors.



Anti-proliferative immunosuppressants

Azathioprine

Azathioprine is a prodrug and is converted to 6-mercaptopurin (6-MP) by the liver.

Uses:

- **Prevent transplant rejection.**
- **Certain autoimmune diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, chronic active hepatitis and some cases of glomerulonephritis).**
- **Owing to its potential toxicity, it is usually reserved for patients in whom glucocorticosteroids alone are inadequate.**

Mycophenolate mofetil

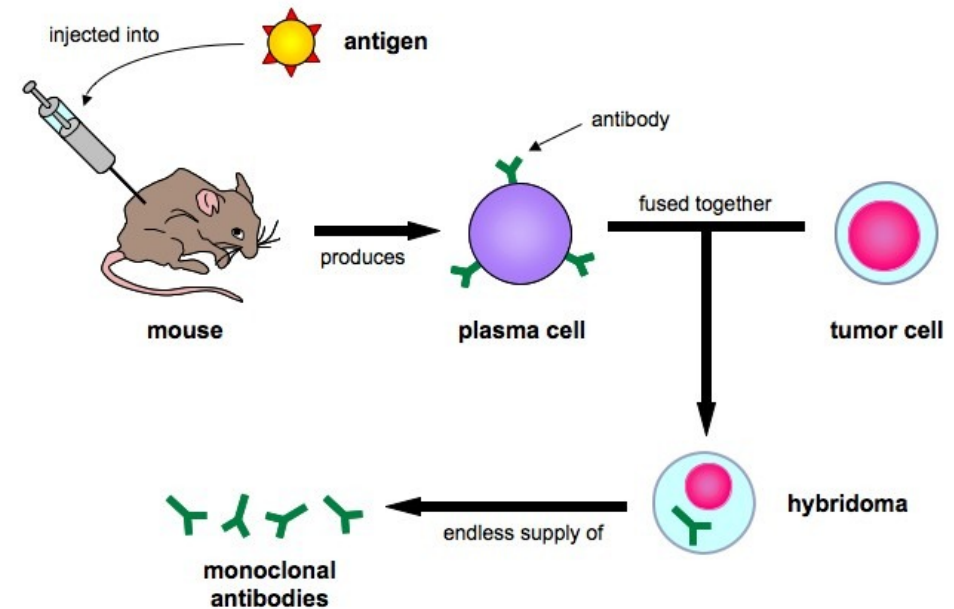
Uses

- **It is an ester of a product of the Penicillium mould.**
- **It is used in combination with ciclosporin and glucocorticosteroids in solid-organ (e.g. renal, cardiac) transplantation and is a more effective alternative than azathioprine.**
- **Mycophenolate mofetil may also be effective in the treatment of other autoimmune disorders, such as **rheumatoid arthritis** and **psoriasis**.**

Biologic immunosuppressants

Monoclonal antibodies

- They are monospecific antibodies that are made by identical immune cells that are all clones of a unique parent cell



Biologic immunosuppressants

Monoclonal antibodies

- **Daclizumab:** (organ transplant rejection) which are anti-IL-2 receptor antibodies, inhibiting IL-2-mediated T-cell activation.
- **Infliximab :** (which bind to TNF-alpha), used in the treatment of **refractory rheumatoid arthritis** and **inflammatory bowel disease**.