IMMUNOMODULANTS AND IMMUNOSUPPRESSENTS

IMMUNOPHARMACOLOGY

- 2 major components of the immune system:
  - **INNATE**
    - Physical – skin, mucus membrane
    - Biochemical – complement, lyzosyme
    - Cellular – macrophages, neutrophils
  - **ADAPTIVE**
    - Antibodies – HUMORAL immunity
    - T-lymphocyte – CELL MEDIATED immunity.

### CHARACTERISTICS OF INNATE AND ADAPTIVE IMMUNITY

<table>
<thead>
<tr>
<th>Innate Immunity</th>
<th>Adaptive Immunity</th>
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</thead>
<tbody>
<tr>
<td>Antigen independent</td>
<td>Antigen dependent</td>
</tr>
<tr>
<td>No time lag</td>
<td>A lag period</td>
</tr>
<tr>
<td>Not antigen specific</td>
<td>Antigen specific</td>
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<tr>
<td></td>
<td>Development of memory</td>
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IMMUNE SYSTEM

- Is designed to protect the host from harmful foreign molecules.
- This system can result into serious problem.
- Allograft introduction can elicit a damaging immune response.
- Immune system include two main arms
  - Cell – mediated immunity.
  - Humoral (antibody – mediated immunity).

IMMUNOMODULATORS
- An **immunomodulator** is a substance (e.g. a drug) which has an effect on the immune system.
- There are two types of effects –
  - Immunostimulation and Immunosuppression.
- Immunosuppressants primarily have the suppressant effect.
- Immunostimulants primarily have the stimulant effect.
- Most drugs however do not have effects on only one receptor, so an immunomodulator may be at the same time an immunosuppressant and an immunostimulant, on different targets within the immune system.

**IMMUNOPHARMACOLOGY**

**ABNORMAL IMMUNE RESPONSES:**

- HYPERSENSITIVITY
- AUTOIMMUNITY
- IMMUNODEFICIENCY

**IMMUNE DISORDERS**

- Hypersensitivities
Exaggerated immune response
- Results in tissue damage
- Autoimmune diseases
- Transplantation rejection
- Immune deficiency

**AUTOIMMUNE DISEASES**

- Pathogenetic mechanisms
  - Loss of immunologic tolerance
  - Activation of autoreactive T and B cells causes acute tissue damage
  - Foreign antigens mimic self
  - Infectious agents produce lymphokines that stimulate autoreactive B cells
  - Influenced by genetic, viral, endocrine, and neuroimmunologlical factors

<table>
<thead>
<tr>
<th>Disease</th>
<th>Autoantigen</th>
<th>Pathophysiology</th>
</tr>
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<tbody>
<tr>
<td>Acute rheumatic fever</td>
<td>Streptococcal cell wall antigens; antibodies cross-react with cardiomyocytes</td>
<td>Arthritis, scarring of heart valves, myositis</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Rh blood group, I antigen</td>
<td>Red blood cells are destroyed by complement and phagocytosis, anemia</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenia purpura</td>
<td>Platelet integrin</td>
<td>Purpura bleeding</td>
</tr>
<tr>
<td>Goodpasture's syndrome</td>
<td>Basement membrane collagen</td>
<td>Glomerulonephritis, pulmonary hemorrhage</td>
</tr>
<tr>
<td>Grave's disease</td>
<td>Thyroid-stimulating hormone receptor</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptor</td>
<td>Progressive muscular weakness</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Cadherin in epidermis</td>
<td>Skin blisters</td>
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</tbody>
</table>

**TRANSPLANTATION REJECTION**

- Allografts from different individuals
- Xenograft from different species
- Tissue rejection may occur by TH cells recognizing different MHC II, aid TC to destroy graft (recognize MHC I)
- T<sub>H</sub> cells also release cytokines, cue macrophages
- Graft vs host disease (bone marrow transplants).

**THERAPEUTIC CONCEPTS**
- Immune system defends and participates in autoimmunity/hypersensitivity/transplant rejection
- Cure/prevention is achieved based on recognition of foreign antigens
- Immune response against self antigens causes autoimmunity/hypersensitivity.

**IMMUNO[HARMACOLOGICAL AGENTS FALL INTO 2 CATEGORIES**
- Those that suppress the immune system
- Suppression overcomes rejection of organ/tissue transplantation and reduces effects of autoimmune diseases
- Those that stimulate the immune system
- Stimulation enhances activity of immune system against infectious agents and neoplastic cells.

**GENERAL PRINCIPLES REGARDING IMMUNOSUPPRESSION**
- Primary responses are suppressed more easily than secondary responses (memory)
- Immunosuppressive agents have different effects on different immune reactions
- Suppression is more effective when therapy precedes exposure to the immunogen

**IMMUNOSUPPRESSIVE AGENTS**

- **T-cell blockers**
  - CYCLOSPORINE
  - TACROLIMUS
  - SIROLIMUS

- **Glucocorticoids**
  - CORTICOSTEROIDS
  - CYCLOPHOSPHAMIDE
  - AZATHIOPRINE
  - MYCOPHENOLATE MOFETIL
  - METHOTREXATE
  - ANTIBODIES

**IMMUNOSUPPRESSANT DRUGS**

  - Inhibitors of cytokine (IL-2) production or action:
    - Calcineurin inhibitors
      - Cyclosporine
      - Tacrolimus
    - Sirolimus (rapamycin).

  - Inhibitors of cytokine gene expression
    - Corticosteroids

  - Cytotoxic drugs
    - Inhibitors of purine or pyrimidine synthesis
      - Azathioprine
      - Mofetil
      - Leflunomide
      - Methotrexate

  - Alkylating agents
- Cyclophosphamide
  - Immunosuppressive antibodies
- that block T cell surface molecules involved in signaling immunoglobulins
  - Anti-lymphocyte globulins (ALG).
  - Anti-thymocyte globulins (ATG).
  - Rho (D) immunoglobulin.
  - Basiliximab
  - Daclizumab
  - Muromonab-CD3
  - Interferon
  - Thalidomide
    - Inhibitors of cytokines (IL-2) production or action
  - Inhibitors of cytokines (IL-2) production Calcineurin inhibitors
    - Cyclosporine
    - Tacrolimus
  - Inhibitors of cytokines (IL-2) action
- Sirolimus (rapamycin).

**CYCLOSPORINE**

- Chemistry
  - Cyclosporine is a fungal polypeptide composed of 11 amino acids.
- Mechanism of action:
  - Acts by blocking activation of T cells by inhibiting interleukin-2 production (IL-2).
  - Decreases proliferation and differentiation of T cells.
  - Cyclosporine binds to cyclophilin (immunophilin) intracellular protein receptors. Cyclosporine-immunophilin complex inhibits calcineurin, a phosphatase necessary for dephosphorylation of transcription factor required for interleukins synthesis (IL-2).
  - Suppresses cell-mediated immunity.

**USES OF CALCINEURIN INHIBITORS (T-CELL BLOCKERS)**

- Cyclosporine commonly used with prednisone and other immunosuppressants to prevent allograft rejections in renal, hepatic and cardiac transplants, and in treatment of RA and psoriasis
o use is delayed post-transplantation due to neurotoxicity concerns

- **Tacrolimus** is approved for prevention of solid-organ allograft rejection, and eczema (topical)
  o treatment begins prior to surgery, and is maintained well afterwards

- **Corticosteroids**

  MOA:
  o inhibit T-cell proliferation & T-cell dependent immunity
  o Inhibit expression of genes encoding cytokines
  o Inhibit production of inflammatory mediators

  Affects cell-mediated immunity more than humoral immunity

- **Continuous administration:**
  o ↑ fractional catabolic rate of IgG

- **Indications:**
  o Autoimmune disorders
    - autoimmune hemolytic anemia, LE
      ▪ Inflammatory Bowel Diseases, Hashimoto’s
    o Modulate allergic reactions - asthma
    o Organ transplantation – rejection crisis

- **Immunosuppressive dose:**
  10-100 mg/day

- **Adverse effects:**
  GI bleeding
  adrenal suppression
  fluid retention
  diabetes
  proximal muscle wasting
  super-infections

**GENERAL PRINCIPLES REGARDING IMMUNOSTIMULATION**

- Stimulating cellular and/or humoral immunity should benefit people with immune deficiencies
- Degree of stimulation relatively small

**TYPES OF IMMUNOSTIMULANTS**
TYPES OF IMMUNOSTIMULANTS

- Bacteria-derived products
- Synthetic drugs
- Cytokines
- Intravenous immune globulin (IVIG)
- Immunostimulatory MAbs

- BCG
- Levamisole,
- ILs, CSFs, TNFs, IFNs
- IL-2
- IFN-γ
- G-CSF

IMMUNOMODULATORS

LEVAMISOLE:
- antiparasitic agent
- other uses:
  > hodgkin’s lymphoma
  > RA

IMMUNOPHARMACOLOGY

IMMUNOMODULATORS

- BCG (Bacille-Camille-Guarin):
  - immunization against tuberculosis

- HIV:
  - Inosiplex
  - Diethylcarbamate (DTC)
- DiGeorge Syndrome of T cell deficiency
  - give THYMOSIN

REFERENCES
• Basic and clinical pharmacology, 11th edition, Bertran G Katzung, Susan B Masters, Antony J Trevor. pg 981_986

THANKYOU