CHAPTER 19

IMMUNO-PHARMACOLOGY

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Ch.Id:-ASU/NSP/EB/HOP/2022/Ch-19

DOI: https://doi.org/10.52458/9789391842529.nsp2022.eb.asu.ch19

The immune system has evolved to protect the host from invading pathogens and to eliminate disease, and the innate and adaptive immune systems work together to provide this protection. The innate immune system, which includes physical (e.g. skin), biochemical (e.g. complement system, lysozymes, interferons), and cellular components, is the first line of defence against invading pathogens (antigens) (e.g. neutrophils, monocytes, macrophages, natural killer cells "NK", natural killer-T cells "NKT"). When the barrier to infection is breached, biochemical components such as lysozymes (which break down the protective peptidoglycan cell wall) and the split products resulting from complement activation destroy the pathogen (e.g. bacteria, fungi, parasites).

Complement components act as opsonins (C3b) and chemoattractants (C3a, C5a) that attract immune cells to inflammatory sites, enhancing macrophage and neutrophil phagocytosis. Complement activation eventually leads to pathogen lysis via the formation of a membrane attack complex, which causes holes in the membrane and cellular component leakage.

Neutrophils and monocytes enter tissue sites from the peripheral circulation during an inflammatory response triggered by infection. The release and action of chemoattractant cytokines (e.g. IL8 "CXCL8," macrophage chemotactic protein-1 "MCP-1; CCL2," and macrophage inflammatory protein-1 "MIP-1; CCL3") from activated endothelial cells and immune cells (mostly tissue macrophages) at the inflammatory site mediates this cellular influx. The adhesion of cell surface receptors on immune cells to ligands on the activated endothelial cell surface triggers it. If these events are successful, the invading pathogen will be ingested, degraded, and eliminated, and the disease will be prevented or shortened.

When the innate immune system is unable to cope with infection, cues from the adaptive immune system are used to activate it. The ability to respond to a variety of antigens, each in a unique way, is one of the characteristics that contribute to this system's success in eliminating pathogens. (2) Differentiate between pathogens that are foreign ("non-self") and host self-antigens. (3) Initiate a vigorous memory response in response to a previously encountered antigen in a learned manner.

- This adaptive response results in the production of antibodies (humoral immunity effectors) and the activation of T lymphocytes (effectors of cell-mediated immunity).
- Professional antigen-presenting cells (APCs), such as dendritic cells (DCs), macrophages, and B lymphocytes, are required for the induction of specific adaptive immunity. Because of their ability to phagocytize or endocytoze protein

antigens and enzymatically digest them to generate peptides, which are then loaded onto class I or class II MHC proteins and "presented" to the cell surface T cell receptor, these cells play a critical role in the induction of adaptive immune responses (TCR).

Whereas a fully functioning immune response can successfully neutralise toxins, inactivate viruses, destroy transformed cells, and eliminate microbes, improper responses can cause extensive tissue damage (hypersensitivity) or reactivity against self-antigens (autoimmunity); alternatively, impaired reactivity to appropriate targets (immunodeficiency) can occur, abrogate essential defence mechanisms.

Note: mAbs (monoclonal antibodies) are subdivided into;

1. **Immunosuppressive mAbs:** eg-antiTNFα (adalimumab, etanrecept, infliximab), IL2Rc antagonists (daclizumab, basiliximab), IL6Rc antagonist (tocilizumab "atlizumab"), CDantagonists (alefacept, muromonab, efalizumab, abatacept), & IgE inhibitor (omalizumab).
2. **Anticancer mAbs:**
    a. Antitumor mAbs e.alemtuzumab, bevacizumab, cetuximab, rituximab, gemtuzumab, trustuzumab.
    b. Isotopes deliver e.arcitumomab, **domains capromab,** ibritumomab **tiuxetan, nofetomob, tositumomab.**
3. **Other:** e.abciximab (PCI), palivizumab **(Respiratory** syncytial virus **"RCV") Immunosuppression**
    1. **Ligands** Immunophilin: **selectively** produces and inhibits: **(function) e.limrolimsporine,** tacrolimus**.**
    2. **Cytotoxic** agents: (immunosuppressive metabolites and alkylating agents) **e. Methotrexate** "MTX", azathioprine "AZT", mycophenolate mofetil, **leflunomide, cyclophosphamide. There are also** others such as hydroxychloroquine, cytarabine, **pentostatin, vincristine** and **vinblastine.**
    3. **Corticosteroids.**prednisone and its **derivatives. ""),**
4. **Immunosuppressive antibodies:**
    1. **Immunoglubin based:** e.g. anti-thymocyte antibodies & anti-lymphocyte
    2. **Immunosuppressive mAbs:** e.g. anti-TNFα (adalimumab, etanrecept, infliximab), IL2-Rc antagonists (daclizumab, basiliximab), IL6-Rc antagonist

(tocilizumab "atlizumab"), & CD-antagonists (alefacept, muromonab, efalizumab, abatacept)

Clinical uses of immunosuppressive agents:

1. **Organ** transplantation (prevents rejection of the transplanted organ or tissue) **e. kidney,** heart, liver and bone marrow.
2. **Autoimmune** diseases **(fetal erythroblasts) and RA.**
3. **Prevent the** cell proliferation: e.g- coronary **stent**
4. **Immunophilin ligand:**

Cyclosporine A peptide antibiotic that acts at the early stage **of antigen receptor-induced T-cell** differentiation and blocks their **activation. It** suppresses **humoral immunity**

MOA: it binds to cyclophilin (IC protein known as immunophilin) forming a **complex that** inhibits calcineurin (cytoplasmic **phosphatase), which is** required for T **cell specific** transcription **factor (NFAT) activation.), participates** in the synthesis of interleukin (e.IL2) by activated T **lymphocytes** (inhibits production **of cytokines).**

It has several immunosuppressive activities, **including**

1. **Reduces** proliferation **of the T cell line** by inhibiting IL2 synthesis and **may decrease the expression of** IL2-RC
2. Reduce induction & clonal proliferation of cytotoxic T-cells from CD8 precursor T-cells
3. Reduce the function of effector T-cells, which are in charge of cell-mediated responses.
4. Some reduction of T-cell dependent B-cell responses.
   - route of administration may be IV & orally, half-life is 27hrs, basically metabolized by CP450-3A & excreted mainly via biliary system.
5. Used for prevention of rejection after organ transplant, severe RA, recalcitrant psoriasis, asthma, endogenous uveitis & severe **keratoconjunctivitis sicca (**dry eye syndrome)
   - Tacrolimus is more potent than cyclosporine, with less rejection episodes, & lower doses of glucocorticosteroids can be used for moderate- severe atopic dermatitis & psoriasis.
   - **Toxicity** same as cyclosporine but neurotoxicity is more severe & not cause gum hyperplasia & hirsutism.

➢ **Sirolimus**

- **MOA:** binds immunophilins & inhibits calcineurin, but doesn't block interleukin production by activated T cells but instead blocks response of T cells to cytokines. It is a potent inhibitor of B-cell proliferation & immunoglobulin production.
- Oral dosage form available only, fast absorbed, only bound to plasma protein & eliminated as a substrate for both CP450 3A & P-glycoprotein.

Uses:

1. Effective both alone & in combination form with others (corticosteroids, cyclosporine, tacrolimus, & mycophenolate mofetil) to prevent rejection of solid organ allografts (approved for renal transplantation).
2. In some dermatologic disorders topically used & combined with cyclosporine in management of uveoretinitis.
3. Sirolimus-eluting coronary stents reduce re-stenosis & additional adverse cardiac events in patients with severe CAD, due to its antiproliferative effects.
4. Everolimus (derivative of sirolimus) is a proliferation-signal inhibitor beneficial in decreasing rejection in cardiac transplantation.

– **Toxicity** includes profound myelosuppression (especially thrombocytopenia), hypertriglyceridemia, diarrhea, headache & hepatotoxicity,

2. Cytotoxic agents:

– Generally, used in combination with immunophilin ligands & corticosteroids.

➢ **Azathioprine**

– Prodrug of mercaptopurine, given intravenously & orally, well absorbed & metabolized primarily to mercaptopurine. Xanthine oxidase splits much of the active form to 6- thiouric acid prior to excretion in urine, so ptatients receiving allopurinol should have reduced dose of azathioprine (1/3 -1/4 of usual dose) to prevent severe toxicity.

– **MOA:** act as antimetabolite by conversion to mercaptopurine & further metabolites that inhibit enzyme involved in purine metabolism. It is cytotoxic in the early phase of lymphoid cell proliferation & has greater effect on activity of T cells than B-cells.

– Used for acute glomerulonephritis, SLE. Severe RA, Crohn's disease, & multiple sclerosis.

- **Toxicity** includes BM suppression (usually leukopenia, anemia & TCP), Skin rash, GI symptoms at higher doses & hepatic dysfunction (very high ALP level & mild jaundice) particularly in patients with preexisting hepatic dysfunction.

➢ **Mycophenolate mofetil**

- Semisynthetic derivative of mycophenolic acid administered as mofetil to enhance bioavailability. It is available orally & IV, 90% excreted in urine.
- **MOA**- hydrolyzed to mycophenolic acid, which acts as an antimetabolite by inhibiting inosine monophosphate dehydrogenase, resulting in purine synthesis inhibition, which suppresses both T and B lymphocyte responses.
- Used as a sole agent in solid organ transplantation (kidney, liver, heart). Also used as an alternative to cyclosporine or tacrolimus in patients who cannot tolerate those medications. Lupus nephritis, RA, and some dermatologic disorders are among the more recent applications.
- Toxicity symptoms include gastrointestinal disturbances (N, V, D, and abdominal pain), headache, hypertension, and reversible myelosuppression (primarily neutropenia).
- Leflunomide is a pyrimidine synthesis inhibitor prodrug. It is orally active, and the active metabolite has a long t1/2 of several weeks, so it is started with a loading dose, but after reaching a steady state, it can be taken once daily.
- Currently approved only for RA, and appears to have antiviral activity.
- Toxicity includes an increase in liver enzymes, which may lead to liver damage, renal impairment, and teratogenic effects.

Cyclophosphamide

A prodrug that is alkylated by a liver enzyme and kills proliferating lymphoid cells. It affects B-cells more than T-cells.

- Effective in the treatment of autoimmune diseases such as SLE, acquired factor XIII antibodies, bleeding syndromes, autoimmune hemolytic anaemia, antibody-induced red cell aplasia, and Wegener's granulomatosis.
- It is toxic in high doses, causing pancytopenia, hemorrhagic cystitis (caused by the urinary metabolite "acrolein"), and alopecia.
- **Corticosteroids**

The first hormonal agents have lympholytic properties, which means they reduce the size and lymphoid content of lymph nodes and spleens while having no toxic effect on

proliferating myeloid or erythroid stem cells in bone marrow.- Glucocorticoids interfere with cell cycle of activated lymphoid cells through:

a. Biochemically, affecting gene expression & ↓synthesis of PGs, cytokines & other signaling molecules that participate in immune response.
b. Cellularly, inhibit proliferation of T-lymphocyte, so suppressing cellular immunity & to lesser extent humoral immunity.
c. Additionally, continuous administration of corticosteroid increases the fractional catabolic rate of IgG, the major class of antibody immunoglobulins, thus lowering the effective concentration of specific antibodies.

- Used for suppressing acute rejection of solid organ allograft & autoimmune diseases e.g. SLE, RA, hemolytic anemia, asthma, nephrotic syndrome & temporal arteritis.
- **Toxicity** includes adrenal suppression, growth inhibition, muscle wasting, osteoporosis, salt retention, glucose intolerance & possible psychosis.

Immunosuppressive Antibodies

Antibodies are made by immunising rabbits with human lymphoid cells or using hybridoma technology, which involves fusing antibody-forming cells with immortal plasmacytoma cells. Antibodies can be mass produced using subcloned stable hybrid cells that produce the required antibody.

- To reduce antigenicity and increase antibody half-life, recombinant DNA technology can be used to humanise the mouse gene by producing chimeric and humanised murine monoclonal antibodies.
- Human patients are given murine antibodies, which cause them to produce human antimouse antibodies (HAMA), which clear the original murine proteins quickly.
- Humanization entails replacing the majority of murine antibody regions with human equivalents while retaining only variable, antigen-specific regions.
- Chimeric mouse-human antibodies have similar properties, but the murine components are not completely replaced. The suffix "umab" or "zumab" for humanised antibodies, and "imab" or "ximab" for chimeric products, is the current naming convention for these engineered substances.

Anti-lymphocyte & Anti-thymocyte Antibodies (ALG & ATG)

- Antisera made by injecting human lymphoid cells into large animals like horses or sheep.

- **MOA**: Antibodies bind to antigen-recognition T-cells, triggering their destruction by serum complement. Instead of blocking antibody formation, they target cellular immunity.
- Used before BM transplantation to prevent graft versus host "GVH" reaction, as well as after BM, heart, and kidney transplantation with cyclosporine or cytotoxic agents or both. ALG is DOC for patients with severe aplastic anaemia who do not have a BM donor or who are too old.
- Hypersensitivity (serum sickness and anaphylaxis), pain and erythema at the injection site, and lymphoma as a late complication are all examples of toxicity.

RhO (D) Immune Globulin Micro-Dose

- Antibodies against red cell Rh0 antigens are found in human IgG preparations.
- If a Rho(D) antibody injection is given to a Rh-negative mother within 24–72 hours of the birth of a Rh-positive infant, the mother's own antibody response to the foreign Rho(D)-positive cells is suppressed because the infant's red cells are cleared from circulation before the mother can generate a B-cell response against Rho(D)-positive cells (D). As a result, she lacks memory B cells that could activate in future pregnancies with a Rho(D)-positive foetus.
- For the prevention of newborn Rh hemolytic disease (erythroblastosis fetalis).

Anti-TNFα (adalimumab, etanrecept, infliximab)

- TNF is bound by mAbs, which prevents it from binding to its receptor on inflammatory cell surfaces, resulting in the suppression of downstream inflammatory cytokines like IL1 and IL6, as well as the adhesion of molecules involved in leukocyte activation and migration.
- **Etanrecept** binds both TNF and TNF, and its MOA differs from others in that it is not fix complement, so it does not lyse TNF-expressing cells, and it binds only active trimeric TNF and lymphotoxin.
- Used to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, ulcerative colitis, and Crohn's disease.
- Side effect: increased risk of tuberculosis, lymphoma, demylination, myocardial and cerebral ischemia, hypertension, and gastrointestinal disorders

IL2-Rc antagonists (daclizumab, basiliximab)

- IL2 receptor antagonists block IL2 binding to activated lymphocytes.
- In renal transplantation, it's used to prevent acute organ rejection.

- Side effect: similar to cyclosporine (some texts state it has negligible S/E eq. to placebo).

➢ **CD-antagonists "anti-CD mAbs"**(alefacept, muromonab, efalizumab, abatacept)

- Inhibit activation of T cells by binding to cell surface CD.
- **Muromonab**, block killing action of cytotoxic T-cells & interfere with other T cell functions.
- Used to treat plaque psoriasis, severe RA, and kidney transplant recipients.
- Side effect: flu-like symptoms, psoriasis exacerbation, and thrombocytopenia.

➢ **Immunomodulating Agents**

Agents that modulate rather than suppress the immune response represent a newer area of immunopharmacology with significant therapeutic benefits in the treatment of immunodeficiency disorders, chronic infectious diseases, and cancer.

Cytokines

- They are a diverse group of proteins with many different functions. Some are immunoregulatory proteins made by lymphoreticular cells that play a variety of roles in immune system function and hematopoiesis control. Cytokines appear to act similarly to hormones in that they mediate their effects through receptors on relevant target cells. Cytokines may also have antiproliferative, antimicrobial, and antitumor properties.
- The serum half-lives of most cytokines (TNF, IFN-, IL2, granulocyte colony-stimulating factor "GCSF," and granulocyte-macrophage colony-stimulating factor "GM-CSF") are extremely short (minutes). Sc administration results in a slower release into the circulation and a longer DOA.

Interferons (INFs)

These proteins have antiviral, immunomodulatory, and antiproliferative properties. There are two types:

- IFN- and IFN- are acid-stable proteins that act on the same receptor on target cells and are usually induced by viral infections, with leukocytes producing IFN- and fibroblasts and epithelial cells producing IFN-.
- Acid-labile protein Type II IFN includes IFN-, which acts on a different receptor on target cells and is usually produced by activated T- lymphocytes.

- IFNs interact with cell receptors to produce a wide range of effects, which vary depending on the cell and IFN type.
    1. IFNs, particularly IFN-, have immune-enhancing properties such as antigen presentation and activation of macrophages, NK cells, and cytotoxic T lymphocytes.
    2. IFNs, particularly IFN-α and IFN- β (which are more potent than IFN-ɣ), inhibit cell proliferation.
    3. MHC molecule expression on cell surfaces induced by IFNs; all three types of IFNs induce MHC class I molecules, but only IFN- induces class II expression.

In glial cells, IFN-β antagonizes this effect & may ↓antigen presentation within the nervous system.

Uses:

1. IFN-α approved for several neoplasms include, hairy cell leukemia, chronic myelogenous leukemia, malignant melanoma, & Kaposi's sarcoma. Also for Hepatitis B & C infections, & shown anticancer activity in renal cell carcinoma, carcinoid syndrome, & T- cell leukemia.
2. IFN-β approved for relapsing-type multiple sclerosis.
3. IFN-ɣ approved for treatment of chronic granulomatous disease.

Toxicity- Fever, chills, malaise, myalgias, myelosuppression, headache, and depression are all side effects that can severely limit their clinical use.

IL2

Originally known as T-cell growth factor, it binds to the IL2 receptor on the surface of responsive cells, causing T- and B-cell proliferation, stimulating macrophage activity, and increasing NK-cell toxicity.

- It's given as an IV bolus, IV continuous infusion, Sc, and IM injection.
- For the treatment of metastatic melanoma and renal cell carcinoma.

Toxicity- Severe hypotension, pulmonary edoema, nephrotoxicity, BM suppression, drowsiness, and delirium are all symptoms of toxicity.

- Colony stimulating factors (GM-CSF) - Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a granulocyte-macrophage colony-stimulating

factor (GM-CSF) that is used to help graft recovery after autologous BM transplant

- G-CSF, a granulocyte colony-stimulating factor used in cancer chemotherapy prophylaxis, caused neutropenia.

Aldesleukin - Recombinant IL2 that activates NK cells and promotes the production of cytotoxic T cells. It's used to treat renal cell carcinoma and lymphoma.

Anakinra - A recombinant form of the naturally occurring IL1 receptor antagonist that prevents IL1 from binding to its receptor, preventing the release of a cascade of cytokines if IL1 binds to the IL1-Rc.

Approved for the treatment of RA in adults who have not responded to DMARDs (disease-modifying anti-rheumatic drugs).

BCG (Bacillus Calmette-Guerin)

- -Muramyl dipeptide is the active component of this attenuated strain of Mycobacterium bovis.
- -Its activity could be due to macrophage activation and improved immune responses as a result.
- Its primary effect on T –cell also can stimulate NK –cells.
- Given ID, IV, Intralesional, Intravesicular & orally with variable doses.
- Used as immunostimulant in treatment of superficial bladder cancer.
- **Toxicity** includes hypersensitivity, shock, fever, & chills.

ISBN- 978-93-91842-52-9