Immunology Lecture – week 14

IMMUNOTHERAPY (Lippincott´s Immunology chapter 18)

Reasons

- I. Increase – stimulation of immunity – in case of immunedefficiency, - in case of necessity to improove the healing process
- II. Decrease – normal immunity – transplantation
- III. Modification – hypersensitivity – therapy of allergy

I. Imunotherapy – to increase immunity

- Therapeutical stimulation of immune functions
- A. ADJUVANCE – non specific immune system stimulation
- B. CYTOKINES – specific stimulation of immune processes
- C. ANTISERA – contain antibodies (normal, hyperimmune)

Immunotherapy is the application of therapeutic treatments for the purpose of increasing or augmenting immune function. Such treatments may include the use of agents (e.g., **adjuvants**) that enhance immune responses in a nonspecific way. More specifically targeted therapies include the application of cytokines that stimulate the activity of particular cell types or the administration of human serum immunoglobulin to supplement or replace suboptimal immunoglobulin levels or isotypes in patients with a variety of immune deficiencies.

A. Adjuvances

- Non specific stimulation of immune reactions
- Adjuvant substances in vaccines – increase effectivity – attraction of APC
  - stimulation of expression of costimulating molecules

BCG – vaccine – stimulise specific but also non specific T cell immunity, (used as adjuvans of other vaccinesn, imunotherapy of bladder tumor – instilation – stimulation of antitumor immunity via inflamatory reaction

Levamisol – antihelminticum, increases cellular immunity. – therapy of Ca of colon – stimulation of antitumor cytokines production by macrophages and T cells

Bacillus Calmette-Guérin (**BCG**), prepared from an inactivated form of *Mycobacterium* and is commonly used around the world as a tuberculosis vaccine, can serve as an effective adjuvant for vaccination or immunization. However, it can also be used directly for postsurgical treatment of superficial bladder cancer. A BCG suspension is periodically instilled into the bladder over a period of six weeks; this promotes inflammation and, in doing so, stimulates antitumor immune responses.

Levamisole, a veterinary antihelminthic agent that provides immunostimulation with low toxicity, has been used in conjunction with other therapies to elevate cell-mediated immunity in a variety of infections. In combination with the cancer chemotherapeutic agent 5-fluorouracil, levamisole is used to treat colon cancer, in which it is thought to stimulate the production of antitumor cytokines and factors by macrophages and T cells.

B. Cytokines

- Regulate – inborne and adaptive immunity,
  - induction and intensity of reactions:
  - cellular growth, differentiation, activation, inflamation and tissue repaire

Interferones -Type I (IFN – α,β) Type II (IFN – γ) – immunetherapy in viral infections – VHB, VHC

Side effects – sever flu-like sy

Innate and adaptive immune responses are regulated by a variety of influences, including cytokines. Cytokines affect the induction and intensity of cellular growth and differentiation, cell activation, tissue inflammation, and tissue repair. Both **type I (IFN- α/β) and type II (IFN-γ) interferons have been used as immunotherapeutic agents to heighten immune responsiveness in patients with viral infections such as hepatitis B or hepatitis C virus. Both natural and engineered interferons are rapidly cleared from the circulation, but their availability can be prolonged by conjugation to polyethylene glycol. Chronic treatment with pegylated recombinant IFN-α decreases the risk of subsequenthepatocarcinoma in about 20% of individuals with chronic hepatitis C viral infection. Additionally, IFN-α2β combination therapy with ribavirin, an antiviral agent, can result in a sustained clinical response in approximately 50% of the cases. Interferons can also be**

effective in treating patients with immune deficiency diseases such as chronic granulomatous disease (CGD, a disease due to defective killing of microbes by phagocytes). The incidence of serious infection is greatly diminished in CGD patients treated with pro-inflammatory cytokines such as recombinantIFN-γ. The most common side effects of interferon therapies are flulike symptoms that can become severely debilitating.

Therapy by cytokines

- IFN-α2b + ribavirin (antivirotckum) – VHC (in 50% influence clinical course of infection cases)
- IFN - γ chronical granulomatouse disease – proinflamatory cytokine

Tumors

- IFN -α hairy cell leukemia
- IL-2 Ca of kidney, melanoma (activation of NK cells)
- IFN – γ, TNF – α tumor of ovaria

Cytokine therapy has also been applied in the treatment of cancer. Immunotherapy against tumors has been traditionally unreliable, and only recently have more reliable treatment regimens been developed. These include the use of IFN-α for treatment of hairy-cell leukemia, IL-2 for treatment of some renal carcinomas and melanomas, and IFN-γ and TNF-α for treatment of ovarian tumors. IL-2 can activate NK cells, an important component for the destruction of tumor cells. Tumors can sometimes outgrow the immune response. An attempt to increase antitumor immune responses has involved the isolation of T cells from excised tumors and their proliferation in vitro by adding IL-2 to the cultures. It is presumed that these T cells (tumor-infiltrating lymphocytes) will include many that are specifically directed against tumor antigens. Proliferation in vitro before reinfusion increases the probability that the cells will encounter their target tumor cells. Exogenous IL-2 may also begiven to the patient to encourage continued proliferation of the antitumor T cells in vivo.

Therapy of immunedefficiency in Ca 1

- Isolation of T cells from TU and their proliferation in vitro by aplication of IL-2 to cell culture
- Production of specific substances against Ca antigens by T cells
- Proliferation of these tumor infiltrationg cells in vitro
- Reinstilation – stimulised cells specifically target tumor. IL-2 can increase proliferation of anti tumor T cells in vivo

Immunetherapy in Ca - 2

- Transfection in vitro
  – infection of TU cell by active gene for cytokines, for expression of different CD molecules
  - changes of TU cells to APC, presenting tumor antigens
  - in vivo cell can cooperate with specific T cell and elicit its activation and tumor cell death
- Cytokine - can act as adjuvans – IL-2 and peptide vaccine against melanoma

C. Antibodies

- Normal human immuneglobulin
- IVIG – intraveouse Ig
  – generalised agamaglobulinemia, hypoglobulinemia
  – from pooled plasma, contains IgG and small amounts of IgM and IgA
  – half time of elimination is 23 days – aplication every one month
  - alteration of production of Ig, of activation of C´ and production of proinflamatory subsatancies

Autoimmune thrombocytopenia, BC-CLL, Kawasaki sy,

- Hyperimune globuline – (anti tetanus, rabies, VHB, VZV, CMV...)
- Monoclonal antibodies – antiepitope Ab – anti CD20 in B-NHL non Hodgkin lymphoma

The administration of **exogenous immunoglobulin** (**human immune globulin**, or **HIg**) can be effective therapy for individuals with generalized antibody deficiencies (hypogammaglobulinemia or agammaglobulinemia). The immune globulin products are typically administered intravenously (**intravenous immune globulin**, or **IVIG**). HIg consists mostly of IgG with trace amounts of IgM and IgA. Because it is derived from pooled immune human sera, it can react against a broad range of epitopes. The benefit provided by HIg lasts for approximately one month (the serum half-life of IgG is about 23 days); therefore HIg injections must be repeated at monthly intervals to maintain sufficient antibody levels for protection. Since HIg is an immunomodulating agent that can modulate complement activation, alter antibody production, and suppress various inflammatory mediators, HIg can be beneficial in situations in which immune deficiency is not the underlying problem. It has been demonstrated to be beneficial in treatment of autoimmune idiopathic thrombocytopenic purpura, B cell chronic lymphocytic leukemia, and Kawasaki syndrome (a disease, usually affecting children, that involves inflammation of the blood vessels and other tissues such as heart muscles). Preparations of immune globulins containing specific antibodies (e.g., against

tetanus, hepatitis B, rabies, cytomegalovirus, and varicella zoster virus) are available for those at high risk or high exposure. With the advent of **monoclonal antibody** technology, large quantities of antibodies against specific epitopes are available for other therapeutic uses as well. For example, monoclonal antibodies against the CD20 marker are particularly useful in treatment of B cell non-Hodgkin's lymphoma.

II. Decrease of immune reactions-1

- Prevention and control of processes responsible for rejection of transplantation grafts, for activation of autoimmune processes

A. Antiinflamatory treatment – corticosteroids, NSAID,

B. Immunesupresive therapy:
Rheumatoid arthritis– inhibítors of TNF α, IL - 1 inhibitors, immunemodulation (methotrexate, azathioprin, imunoadhesines)

NSAIDs have anti-inflammatory, antipyretic and analgesic effects. In addition to providing clinical benefit in the treatment of anti-inflammatory diseases, aspirin is also used to treat conditions requiring inhibition of platelet aggregation. NSAIDs irreversibly block the prostaglandin synthase enzymeIn general, NSAIDs are used clinically to treat mild to moderate pain and inflammatory conditions, such as rheumatoid arthritis.
Aspirin's inhibition of platelet aggregation makes it clinically useful in the prevention of coronary artery thrombosis and transient ischemic attack. The main adverse effects of chronic NSAID use are gastric irritation, erosion, and hemorrhage. Other clinically significant effects include renal tubular necrosis and acute renal failure.
Glucocorticoids have been used for the treatment of rheumatoid arthritis since 1949. This drug is currently widely used to nonspecifically treat many inflammatory diseases and conditions, including autoimmune disorders, allergic diseases, and asthma, and to prevent organ rejection. Glucocorticoids are steroid hormones that bind to the cytosolic glucocorticoid receptor. This newly formed complex then enters into the cell nucleus and binds to the glucocorticoid response elements in the promoter region of the specific gene, causing an increase in expression of the target genes or prevents the expression of the target genes. Glucocorticoids are effective anti-inflammatory agents, although the specific mechanism of their anti-inflammatory effect is not completely understood.

II. Decrease of immune reactions - 2

- Asthma - atopy, IgE, (mastocytes, neutrofils, eosinofils, CD4+Th2)
  - bronchodilatators, theophilin, agonist of β2 - adrenergic receptors ,anticholinergic drugs, antiinflamation drugs(CS), inhibitors of degranulation, monoclonal anti IgE (omalizumab)
- Other autoimmune diseases – humoral or CMI, (Crohn, SM, SLE, myastenia gravis, dermatomyositis, UC, psoriasis, ankylosing spondylitis) – CS, azathioprin, inhibitors of TNF α...

Asthma is a common, chronic inflammatory respiratory disorder. The pathogenesis of asthma involves inflammatory cells such as mast cells, neutrophils, eosinophils, and CD4+ Th2 cells. Inflammation of the bronchi causes bronchial constriction andairway hyperresponsiveness, leading to recurrent dyspnea and episodes of wheezing and coughing in susceptible individuals. Chronic asthma can develop into refractory inflammation of the airways, accompanied by increased bronchial edema, mucus production and bronchial obstruction. Airflow obstruction is often reversible, either spontaneously or following treatment. A predisposing factor in the development of bronchial asthma is **atopy**, the genetic predisposition to develop IgE-mediated responses to common allergens such as mold. Other causes or common triggers of asthma include respiratory infections and animal dander (e.g., from cats).
Treatments for asthma include bronchodilatory agents such as β2-adrenergic receptor agonists (albuterol), methylxanthines (theophylline), and anticholinergic agents (ipratropium bromide); anti-inflammatory agents, such as corticosteroids, inhibitors of mast cell degranulation (e.g., cromolyn), and leukotriene antagonists (zileuton, montelukast, and zafirlukast); and novel immunomodulatory agents, such as omalizumab, a monoclonal anti-IgE antibody.

II. Decrease of immune reactions-3

- Transplantation – usually a certain degree of gene incompatibility – application of therapy to decrease destructive reaction

- Immunesuppression – whole body (irradiation),
  - more specific:
  - *cyclosporin* – inhibition of T cell immunity, selective alteration of regulation of Th cells and production of IL2 + nefrotoxicity
  - *tacrolimus* – derived from macrolid ATB, 50x stronger

Cyclosporine is an essential immunosuppressive agent that was discovered in 1976. It has demonstrated significant efficacy in the treatment of graft-versus-host syndrome after transplantation of bone marrow and other organs and in treatment of some autoimmune diseases. Cyclosporine is a specific inhibitor of T cell–mediated immunity. In vitro studies have shown that it selectively alters the immune regulation activities of helper T cells. Specifically, cyclosporine inhibits calcineurin, which is necessary for the activation of T cells. Therefore, it suppresses the production of IL-2. Clinically significant adverse effects include nephrotoxicity, neurotoxicity, and hepatotoxicity.

Tacrolimus is a macrolide antibiotic derived from the bacterium *Streptomyces tsukubaensis* and is about 50 to 100 times more potent than cyclosporine. Its mechanism of action is similar to that of cyclosporine in that it also selectively alters the activities of helper T cells by inhibiting calcineurin and thus IL-2 synthesis and secretion. Clinically significant adverse effects of tacrolimus are similar to those for cyclosporine, including nephrotoxicity.

III. Modification of immune reaction

- Prevention, interruption of reaction or deviation to less harmfull reaction (allergy, anaphylaxy)

A. Prevention – in case of imminent harmfull reaction
   - 1. ATB – prevention of poststreptococcal sequelaes

B. Modification of on-going process

B Modification of on-going process - to minimalise devastation

1. cytokines
– *IFN* α - therapy of TU,
- *IFN* β – Sclerosis multiplex
- *IFN*–γ atopic dermatitis, decrease production of IL4 and IgE. Side effects – flu-like

- anti HIV therapy – HIV elimination of T CD4+, infection of macrophages, decrease of CD8+: anti HIV therapeutical process *HAART* – to save immunity
IL 2 – stops CD4+ lymphopenia,
IL12 – specific anti HIV CMI,
IL 15 – stimulses CD8+ activity,
IFN-α/IFN-γ – increase activity ofCTL,
GM-CSF – activity of monocytes and macrophages
G-CSF – increase number of myeloid precursors

Cytokines - these protein molecules act as messengers between cells and affect their functions. Systemic administration of cytokines has been used clinically to alter the course of many diseases, including cancer. Clinical research studies support the use of IFNs as treatments for several malignancies as well as other diseases. IFN-α has been used to treat malignant, chronic myelogenous leukemia; Kaposi's sarcoma; hairy cell leukemia; and hepatitis B and C. IFN-β has been used to treat the relapsing type of multiple sclerosis and IFN-γ to treat chronic granulomatous disease. In addition, IFN-γ has also been used to treat patients with severe atopic (IgE-mediated) dermatitis. IFN-γ downregulates IL-4 production and decreases the development of IgE responses. Although the interferons have therapeutic benefits, there are systemic side effects associated with this agent. The most commonly reported side effect is flulike symptoms.

HIV, the virus that causes AIDS, kills CD4+ T cells and reduces the numbers of monocytes/macrophages. CD8+ T cell numbers can also become reduced. Recently, deaths due to HIV infection in developed countries have declined dramatically owing to **highly active antiretroviral therapy (HAART**). However, although the viral load is decreased with HAART, the virus is not eliminated. A number of cytokine therapies are currently being tested in clinical or preclinical trials with the objective of restoring the functional immune cells and preventing opportunistic infections, including the following:

- IL-2 to reverse CD4+ T cell lymphopenia
- IL-12 to enhance HIV specific cell-mediated immunity
- IL-15 to enhance CD8+ T cell function
- IFN-α/IFN-γ to enhance CTL responses
- GM-CSF to enhance monocyte/macrophage function
- G-CSF to increase myeloid cell precursors.

As with most other types of treatments, systemic cytokine therapy is accompanied by adverse side effects. For example, IL-2 supports the growth of T lymphocytes and NK cells but also increases apoptosis in T cell populations. IL-15 also simulates proliferation of both CD8+ and CD4+ T cell populations and appears to be anti-apoptotic.

III. Modificaton of immune reactions

2. Alergen immunetherapy – desensibilisation – subcutaneous application of water extractes of alergen during weaks and months in increasing quantities.
Aim – reduction of alergic reaction, increase of inflamation reaction, inhibition of chronical process
repeated application with alternative application – production of IgG that will bind antigen before it is bound on Fab fragment of IgE anchored on mastocytes (used for alergic rhinitis, asthma, hypersensitivity to insects)
!!!!!!anaphylactic reaction!!!!!!!!!!
20 minutes
carefull survey,
prepared for acute therapy with antihistamines, epinephrine, resuscitation

Allergen immunotherapy involves subcutaneous administration of an aqueous extract of the allergen repeatedly over a period of weeks to months in gradually increasing doses. The objective of allergen immunotherapy is to reduce responses to allergic triggers, decrease inflammatory responses, and prevent development of persistent disease. With repeated immunization, antibody production is redirected from being predominantly IgE to being predominantly IgG. IgG antibodies bind and remove the allergen before it can interact with IgE antibodies bound to the surfaces of mast cells. This treatment is indicated for patients with allergic rhinitis, allergic asthma, or stinging insect hypersensitivity. These patients have symptoms that are not easily controlled by avoiding exposure to an allergen, or pharmacologic therapy for them has not proven to be effective. Allergen immunotherapy is normally safe. However, a serious adverse reaction—anaphylaxis—may develop. All patients receiving immunotherapy should be observed for at least 20 minutes following injection, and emergency treatments, including antihistamine and epinephrine, should be available if necessary.