CANSER (TUMOR) IMMUNOLOGY

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- Normally cells grow and divide to produce new cells in a controlled and orderly manner
- A tumor is defined as a swelling or morbid enlargement that results from an overabundance of cell growth and division.
- They are non- cancerous (benign) or cancerous (malignant).

Benign and Malignant Tumour

- A tumour that grows incapsulated and does not invade the healthy surrounding tissue is benign.
- A tumour that grows uncontrolled invasive, progressive, destructive and that exhibit metastasis is malignant.

Classification of tumours

Malignant tumours or cancers are classified according to the embryonic origin of the tissue from which the tumour is derived.

- Carcinomas are tumors that arise from endodermal or ectodermal tissues such as skin or the epithelial lining of internal organs and glands.
- Sarcomas arise from mesodermal connective tissues such as bone, fat, and cartilage.
- Leukemia, lymphoma and myeloma are malignant tumors of hematopoietic cells of the bone marrow.

- Cancer incidence varies depending on gender, age, heredity, race, geographical location, lifestyle, nutrition, occupation, social conditions, immunological factors, hormones and presence of lesions

Carcinogens

- Radiation: Ultraviolet light, sunshine; X-rays, radioactive elements induce DNA damage and chromosome brakes.
- Chemical: smoke , countless chemicals that damage DNA (mutagens)
- Oncogenic viruses: insert DNA or cDNA copies of viral (v) oncogens into the genome of host target cells.
- Hereditary: certain oncogenes are inheritable.

Effector mechanisms of immunity against tumor

- Macrophage/Dendritic cell attack or antigen presentation
- CD8 cell-mediated cytotoxicity
- Antibody dependent cell mediated cytotoxicity (ADCC)
- Natural killer cells

- The tumors may originate from any nucleated cells. All nucleated cells also excrete MHC class I molecules and thus may present tumor antigens. However, in order to produce a specific response in the T cell, an absolute second signal, namely co-stimulation, is needed. However, tumor cells do not contain these co-stimulatory molecules on their surface.

- Tumor cells do not have MHC class II molecules on their surface that will mediate the formation of an adverse effect in T cell activation. For this reason, usually the host antigen-presenting cells (ASH) present their tumor cells or their antigens on their surface after they are received, and the CTL response occurs when they are recognized on antigen presenting cells. But this answer is often weak and inadequate. Because tumor antigens are weak immunogenic antigens.

Tumor Escape Mechanisms

- Low immunogenicity
- Antigen modulation
- Immune suppression by tumor cells or T regulatory cells
- Induction of lymphocyte apoptosis

- Some tumors stop expression of antigens targeted by the immune system
- Some tumors stop expression of MHC class I molecules. In this case, tumors become unable to present tumor antigens on their surface to CD8 + T cells. Lack of MHC I as a tumor escape mechanism Defects in mechanisms of MHC I production can render cancer cells “invisible” to CD8 cells
- Tumors can escape immunity (and immunotherapy) by selecting for resistant clones that have occurred due to genetic instability

Approaches to Cancer Immunotherapy

- Cytokine manipulations: Cytokines (High Toxicity) IL-2, TNF- α, Interferons
- Tumor vaccines
- Monoclonal antibodies
- Adoptive immunotherapy: T lymphocyte

Tumor Vaccines

- Killed tumor cells
- Purified tumor antigens
- DNA vaccines
- Dendritic cell vaccines

VACCINE AND IMMUNE SERUME

- A different type of immunity, called *passive immunity,* results when a person is given someone else's antibodies. When these antibodies are introduced into the person's body, the "loaned" antibodies help prevent or fight certain infectious diseases. The protection offered by passive immunization is short-lived, usually lasting only a few weeks or months. But it helps protect right away.

Two Types of Immunization

- Passive Immunization
  - Methods of acquisition include natural maternal antibodies, antitoxins, and immune globulins
  - Protection transferred from another person or animal

- Active Immunization
  - Methods of acquisition include natural infection, vaccines (many types), and toxoids
  - Relatively permanent

Acquisition of Passive and Active Immunity

ACQUISITION OF PASSIVE AND ACTIVE IMMUNITY

Type	Acquired through
Passive immunity	Natural maternal antibody
	Immune globulin*
	Antitoxin†
Active immunity	Natural infection
	Vaccines‡
	Attenuated organisms
	Inactivated organisms
	Purified microbial macromolecules
	Cloned microbial antigens (alone or in vectors)
	Multivalent complexes
	Toxoid§

Common Agents For Passive Immunization

COMMON AGENTS USED FOR PASSIVE IMMUNIZATION

Disease	Agent
Black widow spider bite	Horse antivenin
Botulism	Horse antitoxin
Diphtheria	Horse antitoxin
Hepatitis A and B	Pooled human immune gamma globulin
Measles	Pooled human immune gamma globulin
Rabies	Pooled human immune gamma globulin
Snake bite	Horse antivenin
Tetanus	Pooled human immune gamma globulin or horse antitoxin

- The transfer of antibodies will not trigger the immune system

- There is NO presence of memory cells

Standard Immune serum globulin – (gamma- globulin) contains immunoglobulin extracted from the pooled blood of at least 1,000 human donors

- Treatment of choice for preventing measles, hepatitis A and replacing Ab in the immune deficient
- Lasts 2-3 months

Specific immune globulin- prepared from patients against one agent

Contains high titer of specific Ab

- pertussis, tetanus, chickenpox, hepatitis B
- serum produced in horses are available for diphtheria, botulism, spider and snake bites
- act immediately and can protect patients for whom no other useful medication exists

Active immunization

- Natural Infection with microorganism or artificial acquisition (vaccine)
- Both stimulate the proliferation of T and B cells, resulting in the formation of effector and **memory** cells
- The formation of memory cells is the basis for the relatively permanent effects of vaccinations

Active Immunization

- Stimulates the host's immune system to produce specific antibodies or cellular immune responses or both which would protect against or eliminate a disease.
- Active immunity results when a person's immune system works to produce antibodies and activate other immune cells to certain pathogens. If the person encounters that pathogen again, long-lasting immune cells specific to it will already be primed to fight it.

Vaccines

- Provide an antigenic stimulus that does not cause disease but can produce long lasting, protective immunity.

- Edward Jenner in his career he had begun to observe the phenomena of cowpox, a disease common in the rural parts of the western counties of England, and he was familiar with the belief that a person who had suffered from the cowpox could not take smallpox. Finally, in 1796, he made his first experiment in vaccination, inoculating a boy of eight with cowpox, and, after his recovery with smallpox; with the result that the boy did not take the latter disease.

There are 4 main types of vaccines:

- Live-attenuated vaccines
- Inactivated vaccines
- Subunit, recombinant, polysaccharide, and conjugate vaccines
- Toxoid vaccines

Live-attenuated vaccines

- Live vaccines use a weakened (or attenuated) form of the germ that causes a disease.
- Because these vaccines are so similar to the natural infection that they help prevent, they create a strong and long-lasting immune response. Just 1 or 2 doses of most live vaccines can give you a lifetime of protection against a germ and the disease it causes.
- oral polio, yellow fever, mumps, measles, VZV
- tuberculosis (BCG)

The limitations of live vaccines

- they contain a small amount of the weakened live virus, it is dangerous for people with weakened immune systems, long-term health problems, or people who’ve had an organ transplant, pregnant
- They need to be kept cool, Cold chain is necessary for transfer and storage

Inactivated vaccines

- Inactivated vaccines use the killed version of the germ that causes a disease. Use microbes that have been killed, usually by formalin or phenol.
- Inactivated vaccines usually don’t provide immunity (protection) that’s as strong as live vaccines. So you may need several doses over time (booster shots) in order to get ongoing immunity against diseases.
- Inactivated vaccines are used to protect against:
- Hepatitis A, Polio (Salk), Rabies,
- Typhoid, paratyphoid, cholera, plague, pertussis

Subunit, recombinant, polysaccharide, and conjugate vaccines

- Subunit, recombinant, polysaccharide, and conjugate vaccines use specific pieces of the germ — like its protein, sugar, or capsid (a casing around the germ).
- Because these vaccines use only specific pieces of the germ, they give a very strong immune response that's targeted to key parts of the germ. They can also be used on almost everyone who needs them, including people with weakened immune systems and long-term health problems.

- One limitation of these vaccines is that you may need booster shots to get ongoing protection against diseases.

These vaccines are used to protect against:

- Hib (*Haemophilus influenzae* type b) disease, Hepatitis B, HPV (Human papillomavirus), Pneumococcal disease, Meningococcal disease

Subunit vaccines use only those antigenic fragments of a microorganism that best stimulate an immune response. Subunit vaccines that are produced by genetic modification techniques, meaning that other microbes are programmed to produce the desired antigenic fraction, are called **recombinant vaccines**.

For example, the vaccine against the hepatitis B virus consists of a portion of the viral protein coat that is produced by a genetically modified yeast.

- Conjugated vaccines have been developed in recent years to deal with the poor immune response of children to vaccines based on capsular polysaccharides.

Polysaccharide vaccines

- Unique type of inactivated subunit vaccine composed of long chains of sugar molecules that make up the surface capsule of certain bacteria.
- Available for Pneumococcal disease, meningococcal disease and *Haemophilus influenzae* type b

Toxoid vaccines

- Toxoid vaccines use a toxin (harmful product) made by the germ that causes a disease. They create immunity to the parts of the germ that cause a disease instead of the germ itself. That means the immune response is targeted to the toxin instead of the whole germ.
- Toxoids, which are inactivated toxins, are vaccines directed at the toxins produced by a pathogen. The tetanus and diphtheria toxoids have long been part of the standard childhood immunization series.
- Toxoid vaccines are used to protect against: Diphtheria, Tetanus

Combination vaccines

Examples	influenza trivalent OPV, DPT, DPT/Hib, etc. MMR, MMRV PnC/MnC
Advantages:	only one needle at a visit may reduce number of visits reduces costs of administration geographic tailoring
Disadvantages:	loss of immunogenicity due to competition technically more difficult to produce higher production costs higher evaluation costs

INGREDIENTS OF VACCINES

- **Active ingredients**: antigen
- **Added ingredients**:
  - Aluminium: adjuvant
  - Thiomersal, also called Thimerosal: preservative
  - Gelatine: stabiliser to protect live viruses against the effects of temperature
  - Human serum albumin and recombinant albumin: stabiliser
  - Sorbitol and other stabilisers
  - Emulsifiers (to hold other ingredients together)
  - Taste improvers: sucrose

- **Products used in vaccine manufacture and production techniques**:
  - Antibiotics
  - Egg proteins (ovalbumin): This is because the flu virus is grown on fertilised hens' eggs
  - Yeast proteins
  - Latex (in packaging)
  - Formaldehyde: It is used in the production of some vaccines to inactivate toxins from bacteria and viruses
  - Acidity regulators: to help keep the pH balance
  - Human cell-lines, animal cell-lines and GMOs: cell-line for viruses
  - Recombinant DNA technology: This is a technique that uses bacterial or yeast cells to manufacture the vaccine. A small piece of DNA is taken from the virus or bacterium that we want to protect against. This is inserted into other cells to make them produce large quantities of active ingredient for the vaccine (usually just a single protein or sugar).
  - Other growing media: for growing bacteria

Vaccine administration routes

- Intravenous
- Intramuscular
- Oral
- Intradermal
- Subcutaneous

Vaccination can cause side effects

- **Inflammation and anaphylactic reactions** - usually from contaminants in the vaccine preparation-an example being egg proteins in flu vaccine or mercury containing preservatives.
- **Infection** - from improperly inactivated vaccine preparations or the use of a vaccine containing liveattenuated viruses in immunodeficient patients
- **Neurological and autoimmune reactions** - perhaps by rare antigen cross reactions or perturbation of immunoregulatory circuits.

General Rules for vaccination

- Sterile single-use injectors should be used
- Must be applied in the right way
- Cold chain should be observed
- Vaccines that are suspected of being contaminants or not stored under appropriate storage conditions should not be administered.
- Especially live grafts-cold chain applied, sensitive to light
- Lyophilized vaccines should be applied immediately after dilution.

Vaccination Contraindications

- High-fever illness
- Immunosuppressive illness
- Those who have egg allergy (should be asked whether they are allergic to antibiotics and preservatives)
- Live vaccine for pregnancy

	DOĞUMDA	1. AYIN SONU	2. AYIN SONU	4. AYIN SONU	6. AYIN SONU	12. AYIN GÜNÜ	18. AYIN SONU	24. AYIN SONU	İLKÖĞRETİM 1. SINIF	İLKÖĞRETİM 8. SINIF
Hepatit B	I	II			III					
BCG (Verem)			I							
DaBT – İPA – Hib			I	II	III		R			
KPA			I	II	III	R				
KKK						I			R	
DaBT – İPA									R	
OPA					I		II			
Td										R
Hepatit A							I	II		
Su Çiçeği						I				

DaBT – İPA – Hib : Difteri, Aselüler, Boğmaca, Tetanoz, İnaktif Polio, Hemofilus Influenza Tip b aşısı (Beşli Karma Aşı)

KPA : Konjuge Pnömokok Aşısı

KKK : Kızamık, Kızamıkçık, Kabakulak Aşısı

DaBT – İPA : Difteri, Aselüler, Boğmaca, Tetanoz, İnaktif Polio Aşısı (Dörtlü Karma Aşı)

OPA : Oral Polio Aşısı (Çocuk Felci Aşısı)

Td : Erişkin Tipi Difteri – Tetanoz Aşısı

Vaccines that are not yet included in the vaccination scheme (but are licensed and available in our country) include:

- Rotavirus vaccine (RV) (Rotarix, Rotateg)
- Influenza vaccine (IV)
- human papillomavirus vaccine (HPV) (Gardasil, Cervarix)
- Tetanus-diphtheria-acerular pertussis vaccine (Tdap)
- Conjugated meningococcal vaccine. (Mencevax)

Vaccination in Adults

Erişkin Aşılama Şeması

Aşı	18-49 yaş	50-64 yaş	65≥ yaş
Tetanoz, difteri (Td) [1]	Her 10 yılda bir rapel doz aşı		
Kızamık (K) / Kızamık, kabakulak, kızamıkçık (KKK) [2, 3]	1 veya 2 doz aşı		
Hepatit B	3 doz aşı (0, 1, 6. aylar)		
İnfluenza	Yılda 1 doz aşı		Yılda 1 doz aşı
Pnömokok (polisakkarid) [4]	1-2 doz aşı		1 doz aşı
Hepatit A	2 doz aşı (0, 6 -18. aylar)		
Suçiçeği [2]	2 doz aşı (0, 1 ya da 2. aylar)		
Meningokok [5]	1 ya da daha fazla doz aşı		

İmmünitesi ve kontrendikasyonu olmayan tüm bireyleri kapsar.

Risk faktörü olan ve kontrendikasyonu olmayan bireyleri kapsar.

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tetanus, diphtheria: every ten years a booster dose
Pneumococcus: one dose, influenza: every year one dose

Vaccination in Pregnancy

- High risk for live-attenuated vaccine
- Vaccination should be after first trimester. HBV, HAV, pneumococcal vaccines may be administered after 14 weeks if necessary.
- Live and dead vaccinations can be made to the breastfeeding mother when necessary.

Vaccination for healthcare staff

According to CDC recommendations;

- KKK (Measles mumps rubella), VZV
- If there is contact with blood and blood products HBV
- Annual Influenza
- Routinely recommended in adults (T, d and pneumococcal)
- Polio, meningococcal, BCG, typhoid, HAV are recommended for healthcare staff at risk.

Travel Vaccines

- Get information about health conditions and mandatory vaccinations from the Ministry of Health: seyahatsagligi.gov.tr If you have a compulsory vaccination, choose the Travel Health Center nearest you via the website and make an appointment over the phone.
- Whenever you have any of the compulsory vaccinations, the international vaccination center is organized. This report card is now as important as your passport. Do not ignore that you have to have it with you every time you travel abroad

Bacterial infections that prevent with vaccination

- Diphtheria
- Tetanus
- Pertussis
- Typhoid
- Tuberculosis
- Cholera
- Pneumococcal
- Meningococcal infections
- Haemophilus influenza type b (Hib)

Viral Infections Preventable by vaccine

- Measles
- Rubella
- Poliomyelitis
- Mumps
- Flu
- Bird flu
- Swine flu
- Rabies
- Hepatitis A
- hepatitis B
- Small-pox
- Chicken pox
- HPV
- Yellow fever
- rotavirus
- Tick-Borne encephalitis

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