Ministry of Health of Ukraine
Poltava State Medical University

Approved"
at the meeting of the Department of
of Internal Medicine No. 3, Phthisiology
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Minutes № from
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METHODOLOGICAL RECOMMENDATIONS FOR CONDUCTING AND PREPARING FOR PRACTICAL CLASSES

Academic discipline	Clinical immunology and allergology
*Module **4***	Clinical immunology and allergology
Content module	Clinical immunology and allergology
*Topic **№8***	Immunology of tumours. Basic concepts of reproductive immunology. Pseudoallergy.
Course	5
Hours	2

Poltava 2023

Methodological recommendations for the practical training for independent work of students in preparation for the practical training and during the class were prepared by:
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Methodological recommendations were re-approved at the meeting of the Department of Internal Medicine of Internal Medicine №3 with Phthisiology_____
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1. **Relevance of the topic.**

One of the most important problems in immunology is immuno-oncology. It is well known that when the immune system is suppressed, the likelihood of cancer increases by hundreds or thousands of times. The successes of experimental oncology and immunology, as well as extensive clinical experience, have made it possible to achieve significant progress in solving many issues of practical oncology. This is evidenced by the growing number of patients who have been virtually cured of cancer every year.

The success and results of treatment of cancer patients directly depend on the methods of treatment, and most importantly, on the timely diagnosis of malignant tumours. Therefore, the study of immune-dependent mechanisms of tumour development, knowledge of the role of problastoma and antiblastoma factors in tumour onset and growth provides opportunities for timely detection and selection of oncological treatment.

The issue of combating malignant tumours is one of the main issues in modern medicine and is a national task. That is why the development and introduction of new modern methods of immunodiagnostics, immunotherapy and immunoprevention of oncological pathology into clinical practice is one of the most pressing issues in modern medicine.

The general objective: to study the main aspects of immunopathogenesis of cancer, to get acquainted with modern approaches to diagnostics, immunotherapy and immunoprophylaxis of tumours.

Specific objectives:

1. Interpret the immunograms in cancer patients with an assessment of antiblastoma protective factors.

2. To evaluate the results of determination of tumour-associated antigens in the immunodiagnosis of tumours and early detection of recurrence.

3. To prescribe immunotropic therapy in the complex therapy of tumours.

Theoretical questions for the practical session:

1. Etiology and theories of tumour development.
2. The concept of antitumour immunity.
3. Modern approaches to immunodiagnosis of cancer.
4. The concept of tumour-associated antigens.

5. Antiblastomal and problastomal mechanisms of interaction between the host immune system and the tumour.
6. Factors of immunological resistance of the tumour.
7. Modern approaches to the use of immunotropic drugs in the treatment of cancer patients.

General provisions

It is estimated that in a relatively healthy environment, about 10 million mutant cells are formed in the body every day. Mutagenesis increases significantly under the influence of many adverse factors. For example, cytostatics inhibit the activity of natural killer cells (NKs), and ionising radiation and toxic chemicals increase the number of mutant cells.

First of all, it should be noted that the immune system always reacts in a certain way to the appearance of tumour tissue.

The following facts prove this:

- mononuclear cell infiltration of tumours;

- production of antibodies and the appearance of cytotoxic

T-lymphocytes;

- Positive skin tests of immediate type hypersensitivity and delayed type hypersensitivity to the introduction of

of extracts from tumour cells in cancer patients;

- long-term development of tumours (witness tumours);

- cases of spontaneous tumour regression;

- activation of natural killer cells and macrophages.

Against the background of a "positive" immune response directed against the tumour, at a certain stage of development, tumour cells begin to implement defence mechanisms. Malignant cells secrete substances that contribute to the induction of a "negative" immune response in the body, which disrupts the host's immune system.

All tumours can be divided into 3 groups:

1. Highly immunosensitive tumours (e.g. melanoma, kidney and bladder cancer).

kidney and bladder cancer).

2. Medium-sensitive tumours (in particular, colon cancer and

lymphoma).

3. Low-immunosensitive tumours (e.g. breast cancer and lung cancer).

breast cancer and lung cancer).

The tumour forms and grows under conditions of simultaneous deployment of oppositely directed reactions. The dynamics of tumour growth is determined by the balance between immune surveillance factors and problastoma factors that promote tumour growth.

Etiology of tumours

I.1.1. Agents that cause the formation of any tumour are called oncogenes. Those oncogenes that promote malignant transformation are called carcinogens.
I.1.2. Today, it is customary to distinguish 4 groups of oncogenes:
I.1.3. I. Chemical:
I.1.4. I.1. Carcinogenic substances are compounds that probably cause the formation of a malignant tumour or at least increase the incidence of cancer.
I.1.5. I.1.1. Cause either changes in DNA - damage to purine and pyrimidine bases, breaks in polynucleotide chains and formation of cross-links between them - or induce chromosomal aberrations (in particular, chromosome deletions).
I.1.6. I.1.2. Act epigenetically, causing changes in proteins that regulate cell growth.
I.1.7. I.1.3. Act synergistically with viruses (oncogene derepression) or serve as promoters for carcinogenic substances.
I.1.8. I.2. Nutritional oncogenes.
I.1.9. I.3. Hormonal oncogenes:
I.1.10. I.3.1. estrogens;

I.1.13. glucocorticoids.

II. Physical: (various types of radiation that lead to the development of tumours, most likely as a result of direct effects on DNA or through the activation of cellular oncogenes):

I.2. Ultraviolet radiation.

I.3. X-ray radiation.

I.4. Radiation of radioisotopes.

I.5. Radioactive contamination of the area that

leading to internal exposure.

III. Viral diseases:

I.6. Oncogenic RNA viruses: retroviruses

(oncornaviruses).

I.7. Oncogenic DNA viruses (papillomaviruses, Epstein-Barr virus (EBV), hepatitis B virus).

IV. Genetic: (mostly genetic predisposition to the development of neoplasms occurs due to the inherited loss of one or more tumour suppressor genes.

Theories of tumour development

Today, there are two main theories that explain the occurrence of neoplasms - the theory of monoclonal origin and the theory of the "tumour field".

I. The theory of monoclonal origin

According to this theory, the primary carcinogenic agent causes a mutation in only one cell. When the cell divides, a tumour clone is formed, which is the neoplasm. It has been proven that as the tumour progresses, subclones with slightly different properties can develop from the initial clone. This happens as a result of additional genetic changes that occur at any stage of tumour development (the so-called "multiple pushes").

II. The theory of the "tumour field"

A carcinogenic agent, acting on a large number of similar cells, can cause the formation of a field of potentially neoplastic cells. Subsequently, the tumour develops as a result of the proliferation of a certain number of cells within this field. This results in several separate tumours, each of which originates from a specific clonal precursor. The formation of a tumour field can be regarded as the first of several successive stages that lead to tumour development ("multiple starts").

A number of other concepts have been proposed to explain the mechanisms of both tumour monoclonus and tumour field formation.

1.The concept of genetic mutations

Disruptions in the genome caused by heredity, spontaneous action of external agents or mutations can cause neoplasia if genes that regulate cell growth and reproduction are damaged. Tumour transformation occurs as a result of the activation (or deregulation) of specific DNA sequences known as growth-regulating genes, or proto-oncogenes. These genes encode a number of growth factors and their receptors. Activation occurs in several ways:

a) mutation of the proto-oncogene itself;

b) translocation of the proto-oncogene to a more active part of the genome, where regulatory influences activate it;

c) incorporation of oncogenic virus DNA into the active part of the genome;

d) amplification (production of multiple copies of the proto-oncogene);

e) derepression (loss of suppressive control over the existing proto-oncogene).

A permanently functionally active proto-oncogene formed as a result of the above mechanisms is called a cellular oncogene (c-onc). An increase in the production of stimulating growth factors and their receptors, a decrease in inhibitory (suppressor) growth factors, and the production of functionally abnormal factors lead to uncontrolled cell division. Thus, at the molecular level, neoplasia is a dysfunction of growth-regulating genes (proto-oncogenes and suppressor genes that control their activity).

2.The concept of viral oncogenes

Some RNA viruses (retroviruses) contain nucleotide sequences that are complementary to human proto-oncogenes. When reverse transcriptase is activated on viral RNA, DNA is synthesised that already contains sequences identical to proto-oncogenes. These sequences are called viral oncogenes (v-onc). It is assumed that oncogenic RNA viruses acquire v-onc by incorporating the proto-oncogene of the previous host cell into the viral nucleic acid by recombination. This mechanism occurs when the viral DNA is present in the host cell genome (integration stage).

Oncogenic DNA viruses also contain sequences that function as oncogenes and are incorporated directly into the cell genome.

3.Epigenetic concept

According to the epigenetic theory, the main cellular damage occurs not in the genetic apparatus of the cell, but in the mechanisms of regulating gene activity - in growth proteins encoded by growth-regulating genes. Different levels of gene activity responsible for tissue differentiation are determined by hereditary epigenetic mechanisms. The main evidence of the role of epigenetic mechanisms in oncogenesis is found in the formation of tumours under the influence of chemicals that do not affect the genetic apparatus of the cell. The effect of some of these substances is to bind cytoplasmic proteins, changes in which contribute to the emergence of certain tumours.

4.The concept of immune surveillance failure

According to this theory, neoplastic changes occur quite often in the body's cells. As a result of DNA damage, transformed cells synthesise new molecules (neoantigens, or tumour antigens). The body's immune system recognises these neoantigens as "foreign", which leads to a cytotoxic immune response, destroying neoplastic cells. Clinically detectable neoplasms occur only if they are not recognised and destroyed by the immune system in time. This theory is supported by the fact that a high incidence of tumours is observed in immunodeficiencies and in patients receiving immunosuppressive therapy after organ transplantation. The explanation for the predominantly elderly onset of cancer is that old age causes a progressive decline in immune reactivity against the background of numerous DNA repair defects.

The following facts testify against this theory. In mice with a deficiency of the T-cell immune system, the frequency of tumours does not increase. People with immunodeficiencies develop mainly lymphomas, not a full range of different tumours. There is no increase in the incidence of tumours after thymectomy.

Oncogenes and anti-oncogenes

It is important to understand that the activation of only one proto-oncogene is sufficient to enable the autonomous growth inherent in tumour cells. Today, the following main mechanisms of oncogenesis are distinguished:

I. Embedding of a viral oncogene (Chr chromosome; onc-oncogene), for example, retroviruses contain oncogenes scr, myc, ras and erb.

II. Activation of a cellular oncogene by an embedded virus that does not contain oncogenes. Tumour transformation is associated with the exclusion of suppressive effects on the proto-oncogene due to changes in the spatial arrangement of genes.

III. Translocation of genetic material, which leads to activation of an oncogene or formation of a new oncogene from fragments of different chromosomes. In the first case, the translocated oncogene is released from the control of the suppressor gene and is subject to the influence of a constantly working regulatory gene at the new locus. In the second case, a new chimeric gene is formed at the break-junction site, which leads to the synthesis of a chimeric protein (for example, the bcr-abl protein in chronic myeloid leukaemia).

IV. Amplification is an increase in the number of copies of a proto-oncogene. At the same time, suppressor genes are unable to control all available copies (in particular, an increase in the number of copies of the myc gene in nervous system tumours).

V. Mutation of a proto-oncogene, which leads to the synthesis of a mutant oncoprotein. The new oncogene formed as a result of the mutation is devoid of regulatory effects.

VI. Inactivation of the tumour suppressor gene, which causes the constant activity of the normal proto-oncogene.

In recent years, an important link in carcinogenesis has been discovered - disorders in the system of tumour suppressor genes that inhibit the activity of protoncogenes. Their main representative is a gene that controls the synthesis of the p53 protein (the letter p in the name comes from the English word protein, and the number 53 is the molecular weight of the protein, which is 53,000 daltons). The synthesised p53 protein controls the activity of proto-oncogenes, allowing its manifestation only at strictly defined periods of cell life, in particular, when it is necessary for cell division. p53 also controls apoptosis, directing the cell to commit suicide in case of damage to its genetic apparatus. In this way, p53 stabilises the genetic structure of the cell, preventing the emergence of harmful mutations, including tumour-causing ones. The oncogenes of some viruses bind p53 and inactivate it, which leads to the activation of accountable proto-oncogenes and the cancellation of apoptosis, and thus to the accumulation of mutations in the cell, which creates a substrate not only for neoplasia but also for tumour progression.

Features of the surface structures of tumour cells

Oncofetal antigens. All cells have antigens on their surfaces that perform a variety of functions necessary for life support. Several antigens associated with human tumours are present in fetal tissues but absent in the corresponding adult tissues. These are oncofetal antigens. They play an extremely important role in tumour growth. In fetal tissues, these antigens are present in the form of polypeptides, which provide cells with a particularly efficient metabolism. After birth, the genes encoding these polypeptides lose their activity and the synthesis of fetal antigens stops.

In tumour cells, genes that function only in fetal tissues are re-activated. However, unlike fetal antigens, oncofetal antigens are glycoproteins. The carbohydrate residue appears as a result of post-translational glycosylation of fetal proteins. Oncofetal antigens are present in spontaneous, chemical carcinogen-induced and virus-induced tumours. They ensure increased metabolism of tumour cells. The classic oncofetal antigens are α-fetoprotein in hepatocellular carcinoma and cancer embryonic antigen in colorectal malignancies, and their laboratory determination in blood plasma can be used as a screening method.

Specific tumour antigens. So far, very few antigens are known that are present on tumour cells and never appear on normal cells. Such antigens are called specific antigens. It is they that promote the most effective immune response. The most studied are tumour antigens of the MAGE and BAGE genetic families.

Soluble tumour antigens. Some tumour antigens are able to leave the cytoskeleton of the tumour cells and circulate in the internal environment in the form of soluble forms. Such antigens "distract" the immune system, contributing to the unjustified use of immune factors.

Toxin-excretory glycoprotein. Glycoprotein P (permeability) is located in the plasma membrane and serves to remove metabolic toxins from cells. Due to the intensive synthesis of this glycoprotein, tumour cells develop the phenomenon of multiple drug resistance. Malignant tumour cells quickly and efficiently remove chemotherapeutic agents used to destroy them.

Carbohydrates. The structure of carbohydrates, as well as the structure of nucleic acids and proteins, contains important biological information. Carbohydrates have the highest information capacity because they are characterised by the greatest structural diversity. Two identical monosaccharides can form eleven different dicarbohydrates, while two amino acids can produce only one dipeptide. The reading of carbohydrate "words" is based on the variability of sugar subunits, differences in the bonds between them, and the presence of branching points. For example, the set of carbohydrates in

cancer cells differs dramatically from that of normal cells and is a tumour marker. The surface carbohydrates of neoplastic cells contribute to effective metastasis. After penetrating the bloodstream, the tumour cell circulates in the blood for some time. The tumour cell can leave the bloodstream only through the venous wall. Here, they bind to the E-selectins of endothelial cells and leave the blood vessel through intercellular spaces in the endothelium. In this way, the tumour cell enters other organs and tissues, forming metastases. Only 1 in 10,000 cells that leave the primary tumour survive and give rise to a new colony. On their surface, tumour cells have cell-adhesive molecules containing a carbohydrate component (abbreviated CAM), which, when metastasised, attach to the CAM of the organs and tissues with which they have the greatest similarity. The better the capillary network in such organs is developed, the more often metastases occur there. These features determine the typical metastasis of certain tumours to certain organs and tissues. CAM and immunoglobulins have structural homology, so it is believed that immunoglobulins are derived from CAM.

Lectins also play a role in tumour growth. They bind to the surface carbohydrates of cancer cells and mask the tumour from the immune system. On the other hand, blocking the surface structures makes it impossible for them to interact with the tissue matrix, and therefore worsens the conditions for metastasis.

Secondary tumours metastasise more quickly because their vascular network develops as a result of self-induced angiogenesis and is therefore easily penetrable.

Other factors. Tumour cells secrete a factor that stimulates angiogenesis and therefore have a well-developed capillary network. This ensures a sufficient supply of nutrients and growth factors for rapidly proliferating cells. In addition, tumour cells contain more receptors for growth factors. In this regard, they become extremely sensitive to proliferative signals that occur in the body to ensure self-renewal and repair processes. This allows the tumour to maintain intensive cell division.

Cellular mechanisms of anti-tumour immune defence

The role of T-lymphocytes. Cytotoxic T-lymphocytes, or T-killers, are the main element of active anti-tumour defence. Tumour recognition by T-killers is determined by the presence of specific antigens on tumour cells that distinguish them from healthy cells. The ability of T-killers to respond to tumour cells also depends on the expression of HLA class I molecules.

The mechanism of cytotoxic action of T cells is as follows. A T-killer binds to the peptide-HLA class I complex of a tumour cell with its antigen recognition receptor and comes into close contact with it, which requires Mg^{2+} ions. This is followed by

the release of a damaging protein called perforin. Perforin monomers are incorporated into the tumour cell membrane and polymerise in the presence of Ca2+ ions, forming through channels (pathological pores). Through the perforated pores, special T-killer enzymes, granzymes, enter the cell to activate the caspase cascade of target cell self-destruction. Apoptosis can also be induced by another way - through the interaction of a Fas ligand contained on the cytolemma of a T killer with the Fas molecule of a tumour cell. Both of the described effector mechanisms, being quite effective, have a significant drawback, as they require the preservation of the molecular apoptosis system in the tumour cell. It is quite understandable that neoplastic cells, which are characterised by anaplasia, may lose the ability to synthesise components of the caspase cascade, which makes it impossible to induce apoptosis. However, even in this case, the tumour cells are neutralised. The mechanism of destruction is associated with the entry of excessive amounts of water into the cell through the formed stable transmembrane channels. The movement of water is due to the increased osmolarity of the cytoplasm, which is a hypertonic solution compared to tissue fluid. Due to water overload, the intracellular pressure progressively increases and the tumour cell constantly grows in size. At the same time, there comes a time when the membrane tension reaches a critical level and, eventually, the cytolemma ruptures, and the cell contents enter the tissue fluid. Death by this mechanism is called osmotic lysis. It should be noted that through perforated pores, the cell loses important metabolites, which inhibits its metabolism, and also disrupts the physiological ionic asymmetry between the cytoplasm and tissue fluid, which negatively affects the functioning of membrane transport systems. This inhibits the vital activity of the tumour cell, and thus makes it impossible for it to actively counteract the cytotoxic effect. It should be noted that a T-killer is able to destroy only a few tumour cells, after which it depletes its energy and perforin reserves and dies.

Recently, the ways in which type 1 T-helper cells affect malignant cells have been described. They consist in the synthesis of tumour necrosis factors (α and β), which, when interacting with the corresponding tumour receptors (in particular, the p55 receptor), induce cell apoptosis. If this mechanism is ineffective, an alternative pathway is triggered - the release of γ-interferon and the implementation of its antitumour activity. In particular, γ-interferon stimulates natural killer cells and macrophages, which are secondary involved in the immune response against the tumour. In addition, this cytokine suppresses tumour angiogenesis and enhances the expression of histocompatibility molecules (HLA-A), which effectively detect tumour peptides by cytotoxic T lymphocytes. This makes neoplasia more accessible for immunological recognition. The actual contribution of type 1 T helper effector mechanisms to anti-tumour protection is still being investigated.

Natural killer cells. Natural killer (NK) cells are an important element of anti-tumour defence. They do not contain antigen recognition receptors, but select "candidates" for destruction according to the expression of HLA class I molecules. The surface of these cells contains so-called lectin receptors that recognise membrane carbohydrate residues released in transformed cells due to the loss of shielding molecules. However, this stimulus is not enough to activate PCs. The fact is that natural killer cells contain a killing-inhibitory receptor that can interact with HLA I molecules and cancel activation. Therefore, PC exerts its effect only when HLA I molecules are impaired in the target cell, which is typical for tumour cells.

Due to the nonspecificity of recognition, PCs are able to kill neoplastic cells without prior sensitisation to tumour antigens, which involves long (4-5 days) and complex mechanisms of cell interaction involved in the immune response.

The effector mechanism of PCs is the release of perforin monomers, which are incorporated into the cytoskeleton of the target cell, and the introduction of granzymes into the cytoplasm of the tumour cell. PCs, unlike T-killers, do not express Fas ligand.

It is known that tumour cells can stop expressing HLA I to avoid recognition by T-killers. In this case, natural killer cells that perform nonspecific recognition are involved in antitumour defence.

LAK cells. Tumour cells can also be destroyed by activated lymphocytes, the so-called lymphokine activated killer (LAK) cells. LAK cells come from the "zero" population of lymphocytes and are thus similar to natural killer cells. Like natural killer cells, they destroy tumour cells without first recognising specific antigens. In addition, they do not require the presence of HLA I molecules on the target cell. Such cells are obtained artificially by treating a culture of large granular lymphocytes with interleukin 2. It should be noted that large doses of interleukin 2 administered to the body cause a distinct toxic effect, which is manifested by tissue edema. The role of LAC in the natural immune response is being studied.

Macrophages. Tumour cells synthesise a factor that inhibits macrophage migration (abbreviated as MIF, migration inhibitory factor). MIF has two important functions in tumour growth. Under the influence of this cytokine, macrophages that have entered the tumour lose their mobility, while retaining the ability to synthesise biologically active substances. Thus, on the one hand, MIF deprives macrophages of the ability to transmit information about the detected tumour to immunocompetent cells (T-helper cells), and on the other hand, it allows the tumour to use the immobile macrophage as a factory for the production of

plasminogen activator. Thanks to the synthesised plasminogen activator, tumour cells are able to enter the bloodstream and spread throughout the body.

The body's immune response to tumour antigens

Both types of immune response occur to tumour cell antigens: humoral with the appearance of antibodies and cellular with the accumulation of specifically reactive T-killers. Antitumour antibodies not only protect the body against tumours, but can also contribute to their progression due to the amplification effect.

The mechanism of primary recognition of tumour antigens is the least understood aspect of anti-tumour immune defence. It is believed that primary recognition is performed by antigen-presenting cells (APCs). They are known to be activated when pathogen-related molecular patterns of microorganisms are detected. It turned out that the corresponding molecules are also contained in the surface structures of human cells, but they are shielded from recognition. It is believed that during malignant cell transformation, some of these molecules are released, losing their shielding molecules, and become targets for interaction with macrophage pattern recognition receptors. It is likely that changes in surface structures are associated with deep processes of malignant transformation. In particular, it has been established that tumour cells lose the expression of surface sialic acids, which leads to the release of carbohydrate residues (galactose, N-acetylglucosamine, mannose) that are effectively recognised by APCs. Activated macrophages or dendritic cells, through the processing of captured antigens and presentation of immunogenic tumour peptides as part of HLA class II molecules, engage "0" helper T cells in the immune response, which, under additional exposure to IL-12, differentiate predominantly into type 1 helper T cells. Due to the presentation of the same peptides in HLA I, APCs activate antigen-specific, but "naïve" CD8+ T lymphocytes, which subsequently differentiate into immunocompetent T killer cells. Since tumour antigens differ little from conventional autoantigens, there is often a lack of proper expression of costimulatory molecules on APCs, which leads to anergy of CD8+ T cells. In this case, activated type 1 helper T cells release γ-interferon, which enhances the expression of B7 costimulatory molecules (CD 80 and CD86) on APCs. At the same time, T-helper cells secrete interleukin 2, which is an inducer of CD8+ T-cell proliferation. As a result of this effect, CD8+ T cells independently start synthesising IL-2, causing their own division by an autocrine mechanism (blast transformation reaction). An antigen-specific clone of immunocompetent cells called cytotoxic T lymphocytes is formed. The resulting T-killers re-recognise and destroy the corresponding tumour cells. In this case, the recognition of targets is simplified, as it does not require the presence of

costimulators. Each clone of T-cytotoxic cells, which are specifically reactive cells, contains antigen recognition receptors exclusively against a specific tumour antigen and therefore has a highly targeted effect. The number of lymphocytes of a clone usually correlates with the degree of expression of the corresponding tumour antigen. All this ensures the most adequate antitumour effect.

Since activated APCs synthesise mainly IL-12, the immune response is cell type-specific, but not limited to it. The resulting type 1 T-helper cells synthesise γ-interferon, tumour necrosis factors α and β, and interleukin 2, each of which has a known antitumour effect. These cells secondary involve macrophages in the immune response to the tumour (in this case, macrophages function as effector cells).

It is known that tumour cells often stop expressing HLA I molecules to avoid the cytotoxic effects of T-killers. In this case, they become targets for natural killer cells, which perceive the absence of HLA I molecules as a signal to exert a killing effect. The action of PCs is to trigger apoptosis in a compromised cell or destroy it by osmotic lysis. The recognition of tumour cells and the effector response are nonspecific - they are identical to those affected by the virus. As a result of the work of PCs and T-killers, fragments of dead tumour cells are released, which are captured by dendritic cells or phagocytosed by macrophages, which ensures the maintenance of the immune response.

Morphological manifestations of the immune response to tumour antigens are expressed in the accumulation of immunocompetent cells in the stroma and along the tumour periphery: T- and B-lymphocytes, as well as plasma cells and macrophages. Clinical and morphological observations indicate that in cases of pronounced cellular infiltration of the tumour stroma, a relatively slow development of the tumour is observed. Tumours with a complete absence of immunocompetent cells in the stroma grow faster and metastasise early.

At the initial stages of tumour development (before metastases occur), signs of antigenic stimulation are observed in the regional lymph nodes. They are manifested in hyperplasia of lymphatic follicles with an increase in the size of proliferation centres and hyperplasia of reticular and histiocytic elements along the sinuses (the so-called sinus histiocytosis), which are considered as manifestations of antitumour protection and a favourable prognostic sign. Clinical manifestation of the tumour is possible in case of failure of the immune response.

The following reasons for this situation are identified (according to R.V. Petrov):

1) tumour growth-enhancing effect of circulating antitumour

antibodies;

2) blockade of specific "antitumour" receptors on the surface of lymphocytes by tumour antigens and immune complexes circulating in the blood.

Today, the influence of immune tolerance on the effectiveness of antitumour immunity cannot be ruled out, since tumour cells usually retain most of the familiar antigens of the source tissue, to which immune tolerance is effectively maintained. Due to the synthesis of soluble antigens by the tumour, it is possible to induce "low-dose" tolerance. In addition, it has been found that with an increase in the size of the tumour, there is a gradual decrease in immune reactions against it, which is also considered a kind of immune tolerance. Certain importance is attached to genetically determined weak (or absent) reactions to certain tumour antigens, as well as insufficient immune surveillance by the thymus.

Immunotherapy of tumours

Modern immunotherapy includes a wide range of drugs, the main groups of which are represented by microorganisms and their components, thymus preparations, cytokines (natural and recombinant), polysaccharides and peptides. Genetic engineering methods are becoming increasingly common.

Monoclonal antibodies rapidly entered immunology in the late 70s. It was assumed that the developed technology of producing immunotoxins (antibodies with toxic compounds attached to them) for direct and indirect effects on the tumour or for activating T-killers should provide specific immunotherapy for tumours. However, there are only a few cell surface antigens that could serve as more or less specific targets for antibodies. These include, for example, cancer embryonic antigen in colon tumours or idiotypic antigenic determinants of immunoglobulins in B-cell lymphomas.

However, monoclonal antibodies play a major role in the immunophenotyping of haemoblastosis. They are equally effective in immunodiagnostics for serological markers of tumours. The closest thing to immunotherapy is the work on detecting the location of tumours and metastases using monoclonal antibodies or their active fragments labelled with radioactive isotopes. In this way, small metastases in the body can be detected, and in some cases, therapeutic doses of radioisotope can be concentrated in the tumour or metastases. The cancer embryonic antigen was used as a target in these studies. Malignant tumours of the colon and thyroid gland are the

richest in it. However, these studies, despite their serious scientific nature, have not yet been put into practice.

T-lymphocytes infiltrating a tumour. T-cell-based immunotherapy of tumours received a powerful impetus for development in the work of S. Rosenberg, who proved the therapeutic effectiveness of T-cell growth factor (interleukin 2) in metastatic melanoma and some other tumours. He used tumour infiltrating lymphocytes (TILs), activating them with IL-2, and injected them into patients along with this cytokine. TILs are nothing more than activated cytotoxic T-lymphocytes and natural killer cells that have already entered the tumour at the time of sampling and destroy its cells. The approaches proposed by Rosenberg are used in the clinic, albeit to a very limited extent due to the high toxicity of the growth factor and the unpredictability of the effect in specific situations. However, this work was the beginning of the use of cytokines for therapeutic purposes, as well as the search for anti-cancer vaccines based on cytokines.

Gene therapy of tumours. Recently, the great successes of genetic engineering have led to the development of a new field - gene therapy of tumours. It is based on the creation of so-called anti-cancer vaccines. They can be obtained by introducing new genes into the genome of a tumour cell: genes for antitumour cytokines and their receptors, tumour-associated antigens, suicidal genes, foreign antigens, and viruses.

One of the main areas of gene therapy is the development of vaccines that contain tumour cells that synthesise cytokines that inhibit cell division. This creates a high concentration of protective cytokines in the tumour area and significantly reduces the toxicity of the latter to the body. In recent years, dozens of papers have been published that provide experimental data on the antitumour effect of recombinants that produce almost all cytokines.

A promising approach to the development of anti-cancer vaccines is to produce hybrid proteins consisting of tumour-associated antigens and cytokines. It is known that the immunogenicity of tumour-associated antigens is low, because they are basically normal proteins whose production only increases in tumour cells. Cytokines can enhance the immunogenicity of the latter and increase the sensitivity of tumour cells to the cytotoxic effects of T-killers.

Another area is the use of so-called suicidal genes, such as the herpes simplex virus thymidine kinase gene. Thanks to the latter, tumour cells acquire the ability to phosphorylate the acyclic nucleoside ganciclovir, which is used to treat herpesvirus infections, resulting in the death of these cells under the influence of an antiherpetic drug to which they are normally insensitive.

Test tasks:

1. What agents are called "carcinogens"?

1) those that can cause the formation of any tumours;

2) those that cause malignant transformation;

3) all groups of oncogenes;

4) a group of viral oncogenes;

5) group of physical oncogenes.

2. What are the processes underlying the emergence of the tumour process according to the theory of monoclonal origin?

1) the effect of a carcinogenic agent on a large number of similar cells and the formation of a field of potentially non-plastic cells;

2) the mechanism of tumour formation has not been fully elucidated;

3) the primary carcinogenic agent causes a mutation in only one cell, which divides to form a tumour clone;

4) all of the above processes are reflected in this theory.

3. What role do proto-oncogenes play in tumour transformation?

1) proto-oncogene activation causes tumour growth;

2) proto-oncogene activation blocks the possibility of tumour growth;

3) proto-oncogene deactivation stimulates tumour growth;

4) proto-oncogenes do not play a role in tumourigenesis.

4. Which surface structures of tumour cells are present in germinal tissues but absent in the corresponding adult tissues?

1) specific tumour antigens;

2) soluble tumour antigens;

3) oncofetal antigens;

4) cell adhesive molecules containing a carbohydrate component (CAM);

5) no such surface structures exist.

5. What cellular mechanisms perform nonspecific recognition of tumour cells?

1) cytotoxic T-lymphocytes;

2) natural killer cells (NK cells) and LAK cells;

3) complement system;

4) anti-tumour antibodies (immunoglobulins);

5) all of the above.

6. What cellular mechanisms are involved in the specific recognition of tumour cells?

1) natural killer cells (NK cells);

2) antigen-specific immunoglobulins (tumour-specific antibodies);

3) complement system;

4) cytotoxic T-lymphocytes;

5) all of the above mechanisms.

7. Which of the following refers to the factors of tumour immunoresistance?

1) low immunogenicity of tumour antigens;

2) change of antigens during tumour progression;

3) appearance of soluble antigens associated with the tumour;

4) ability to induce apoptosis of cytotoxic T-lymphocytes;

5) all of the above.

8. Which of the factors of immunoresistance of tumour cells prevents specific recognition of the tumour by T-killers?

1) termination of expression of class I histocompatibility molecules on the surface of tumour cells;

2) expression of "trap receptors" by tumour cells;

3) rapid catabolism of antibodies on the cell membrane;

4) selection of immunocompetent tumour cells;

5) appearance of cellular receptors for various growth factors and growth-promoting cytokines.

9. Which of the modern methods of tumour immunotherapy is most widely used in oncology?

1) monoclonal antibodies;

2) T-lymphocytes infiltrating the tumour;

3) gene therapy of tumours;

4) cytokine therapy of tumours;

5) the use of agrochemicals with specified properties.

10. Immunoprophylaxis of tumours caused by which of the following viruses has become widely used?

1) papilloma virus (HPV);

2) T-cell lymphoma virus;

3) Epstein-Barr virus;

4) herpes virus (KSHV);

5) hepatitis B virus (HBV).

Correct answers:

1. 2)
2. 3)
3. 1)
4. 3)
5. 2)
6. 4)
7. 5)
8. 1)
9. 4)
10. 5)