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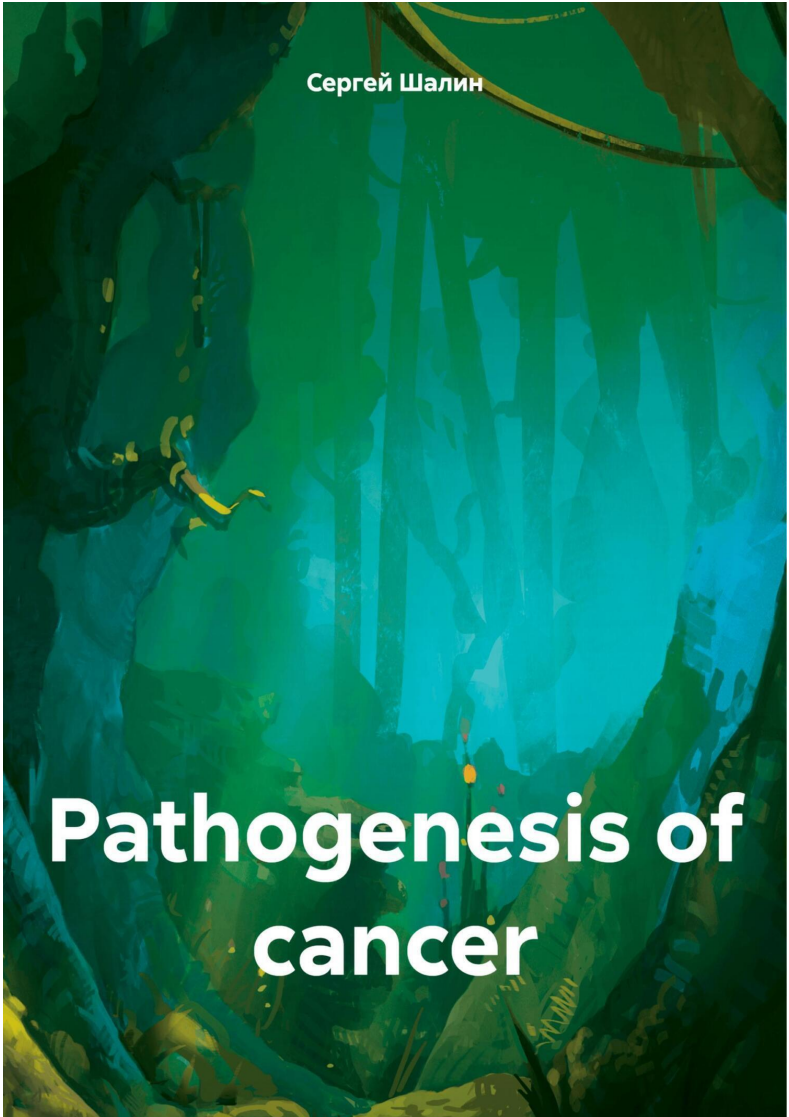

Pathogenesis of cancer

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Аннотация

This article is devoted to the pathogenesis of cancer. The processes of cancer cell formation are briefly described.

Содержание

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We can talk about the pathogenesis of cancer only by determining the primary mutation of the nuclear DNA of the genome of the precursor cell of the cancer cell. It is possible to theoretically substantiate which cell can lay claim to the role of a precursor cell of a cancer cell if we take into account the functional abilities of the cancer cell received from a somatic cell and the pathological state of the tissues that created optimal conditions for the emergence of a malignant stem cell, the growth and development of the malignant process. Key words: initiation, promotion, monocyte, malignant stem cell, mutation.

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INTRODUCTION

Carcinogenesis or oncogenesis is a multi-stage mechanism of the emergence, growth and development of a malignant process. According to the modern theory of carcinogenesis, the occurrence of a malignant tumor is the result of the sequential accumulation of mutations in the somatic cells of the body that are not inherited. When the number of mutations becomes critical, the formation of a primary malignant stem cell occurs. The weak link of this theory is the absence of a cancer cell precursor cell. In a morphological study, it looks like this: a healthy normal cell, next to it a malignant cell, there is no transitional variant or precursor cell to a cancer cell.

MALIGNANT DISEASES

All human malignant diseases are divided into two main groups: hemoblastoses and solid tumors. The principle of division is based on the different localization of the malignant process and some similarity between malignant cells and normal cells of the microenvironment. The cytogenesis of malignant diseases of hematopoietic and lymphoid tissue is considered the most studied, which is based on the doctrine of stem and semi-stem precursor cells of hematopoiesis. Cytogenesis of solid tumors has not yet been studied; there is no clear idea from which progenitor cells malignant cells arise. That is why we will mainly consider issues related to solid tumors, drawing a possible analogy with hemoblastoses.

General signs of hemoblastoses and solid tumors.

1. Etiology: chemical agents (endo- and exocarcinogens), ionizing radiation.

2. Pathogenesis: nuclear DNA mutations and epigenetic changes – damage to the structure of the cell membrane and chemical processes in the cytoplasm of the cell. 3. Diagnostics: clinical, laboratory and instrumental research methods with mandatory morphological verification of the diagnosis (histological and cytological studies).

4. Complications: infectious, thrombotic, disruption of the normal mechanism of osteogenesis, gastrointestinal

complications (nausea, vomiting, hiccups, constipation, diarrhea and mucositis), intoxication and psychological changes (anxiety, depression, aggressiveness and suicide).

5. Principles of pathogenetic therapy: influences that suppress the proliferation of malignant cells (X-ray, chemotherapy, hormone therapy and immunotherapy); vitamin therapy; auxiliary therapy (blood transfusion, relief of infection, treatment of thrombosis and bleeding); bone marrow transplantation.

6. Causes of death: cachexia, secondary infection, severe anemia, thromboembolic complications, massive bleeding and hemorrhage.

7. The main symptoms of a malignant neoplasm: transmission of all properties by inheritance, preservation of the principle of malignant progression, uncontrolled cell division, invasive growth and metastasis. Thus, the general similarity of hemoblastoses and solid tumors is established at the genetic level. General signs of hemoblastoses and solid tumors.

Differences between haemoblastosis and solid tumours

Let us consider each group of malignant diseases separately and also split haemoblastosis into two sub-groups: leucosis and lymphoma. Based on studies of the onsets of all malignant diseases, we can draw the following conclusions:

Leucosis is a numerous and heterogeneous group of malignant diseases, which emerge from haemopoietic (blood forming) cells and affect red marrow.

– the precursors of malignant stem cells are pluripotent or unipotent stem cells of the foci of myelo- or lymphopoiesis in the red marrow;

– both stages (initiation and promotion) of the "birth" of a malignant stem cell take place in the same location – in the red bone marrow;

– the basis of a malignant stem cell "birth" is the block of differentiation and transformation of a pluripotent or unipotent stem cell of myelo- or lymphopoiesis;

– the mechanism of a malignant stem cell "birth" lies in the genotype and epigenetic changes of a pluripotent or unipotent stem cell of myelo- or lymphopoiesis following the carcinogenic impact;

– the malignant process starts from the "birth" of one malignant stem cell, which then forms a clone of malignant cells;

– the disease is manifested through growth of the malignant process in the red marrow, but at that time a primary malignant focus is absent;

– the malignant process develops by the proliferation of malignant cells within the red marrow, and by haematogenous and lymphogenous spread in the host body;

– the malignant process impacts haemopoiesis, homeostasis, immunity etc.

Lymphoma is a group of malignant haematological diseases of lymphatic tissue characterised by malignant transformation of lymphoid cells;

– the precursors of malignant stem cells are pluripotent or unipotent stem cells of lymphopoiesis located in the red marrow;

– the first stage (initiation) of the "birth" of a malignant stem cell takes place in the red marrow, the second stage (promotion) in the location of the primary malignant focus;

– the basis of a malignant stem cell "birth" is a block of differentiation and transformation of a pluripotent or unipotent stem cell of lymphopoiesis;

– the mechanism of a malignant stem cell "birth" is the genotype and epigenetic changes of a pluripotent or unipotent stem cell of lymphopoiesis following the carcinogenic impact;

– the malignant process starts from the "birth" of one malignant stem cell, which then forms a clone of malignant cells;

– the malignant process is manifested through forming the primary malignant focus located in the lymph nodes (nodal involvement) or in any other organs and tissues (extra nodal involvement);

– the malignant process is developed by lymphogenous spread in the host body, sometimes cells of lymphoma are detected in the blood, but usually they tend to form thick tumours in the lymphatic system or in the internal organs (liver, stomach, nervous system or in other places);

– the malignant process impacts haemopoiesis, homeostasis, immunity etc.

Solid Tumours are the largest in quantity, heterogeneous group of malignant diseases, which develop through multi-stage

malignant transformation of a normal proliferating somatic cell into a malignant stem cell:

– the origins of malignant cells are not known, as the precursor of the malignant stem cells is not known. It is supposed that the precursors are normal somatic proliferating cells – cambial cells, which are located in the area of the crypts' floor, glands' neck, periosteum and perichondrium, along the blood vessels' flow and also in the area of intense restorative proliferation;

– it is not known where and how both stages (initiation and promotion) of the "birth" of a malignant stem cell take place. It is supposed, in the area of intensive proliferation of cells;

– also it is not known what process underlies the "birth" of a malignant stem cell. It is supposed that a normal somatic proliferating cell transforms into the malignant stem cell;

– the mechanism of the "birth" of a malignant stem cell is not known. It is supposed that following the carcinogenic impact the genotype and epigenetic changes of a normal proliferating somatic cell take place, and these are a launching mechanism for its transformation into the malignant stem cell;

– a malignant focus starts with the "birth" of one malignant stem cell (in 80% cases), two or more malignant stem cells (20%), which then form a clone of malignant cells;

– the malignant process is manifested through forming the primary malignant focus, which can be located in different organs and tissues, and it increases by proliferation of cells, appositional and invasive growth;

– the malignant process is developed by the haematogenous and lymphogenous spread in the host body while forming the secondary foci – metastases;

– the malignant process impacts haemopoiesis, homeostasis, immunity etc.

Thus, the contemporary notions:

1. The difference between haemoblastosis (leucosis and lymphoma) on the one hand and solid tumours on the other, is in the mechanism of the "birth" of a malignant stem cell;

– in the case of haemoblastosis, following the carcinogenic impact the genotype and epigenetic changes of a pluripotent or unipotent stem cell of myelo- or lymphopoiesis, a block of differentiation and its transformation into a malignant stem cell take place;

– it is supposed that in the case of solid tumours, following the carcinogenic impact genotype and epigenetic changes of a normal proliferating somatic cell take place, which are a launching mechanism for its transformation into a malignant stem cell.

2. The difference between leucosis on the one hand and lymphoma and solid tumours on the other, is in the manifestation of the malignant process:

– in the case of leucosis, the disease manifests itself by the affection of the red marrow, but the primary malignant focus is not formed. The "birth" of a malignant stem cell requires 2-4 genotype alterations of the nuclear DNA of a pluripotent

or unipotent stem cell of myelo- or lymphopoiesis. Epigenetic alterations are of secondary importance, that is why changes in the living conditions and microenvironment of the precursor are not a prerequisite;

– in the case of lymphoma and solid tumours, the disease manifests itself by necessary forming of the primary malignant focus. The "birth" of a malignant stem cell requires 7-8 genotype alterations of the nuclear DNA of the precursor of the malignant stem cell. The genotype and epigenetic alterations are of equal importance, that is why changes in the living conditions and microenvironment of the precursor are a prerequisite. The large number of genotype alterations of nuclear DNA and the equally important genotype and epigenetic alterations determine the length of pre-clinical evolution of the disease.

3. The features of tumorous growth of lymphoma are common with those of solid tumours – they form the primary malignant focus and metastasis, as well as with leucosis; they can form the states, which are analogous to lymphoid leucosis. That is why the lymphoma is considered as an intermediate variant of the malignant process development.

4. Given that in the case of haemoblastosis the first stage (initiation) of the "birth" of a malignant stem cell takes place in the red marrow, it would be logical to suppose that in the case of solid tumours the first stage (initiation) of the precursor of a malignant stem cell also takes place in the red marrow. So the following second stage (promotion) occurs in the organs and

tissues where the “birth” of a malignant stem cell takes place and it forms the primary malignant focus.

ONCOGENESIS

The basis for the growth and development of oncogenesis is a malignant stem cell, and the basis for the "generation" of a malignant stem cell is the return of a tissue Monocyte, which has genotypic and epigenetic changes, to the embryonic state during mitosis, a differentiation block at the pluripotent or unipotent level and transformation. Monocyte – with a diameter of 16–18 microns, various morphological variations in the nature and intensity of coloring of the nucleus and cytoplasm. The kernels may approach round, bean-shaped shapes. The cytoplasm is grayish or pale blue in color and may contain numerous dust-like azurophilic granules. Differentiation of Monoblast into Monocyte occurs in the red bone marrow within 5 days. A monocyte stays in the bone marrow for an average of 3 days, then divides and, without forming a bone marrow reserve, enters the peripheral blood. In the blood, the Monocyte is the largest blood cell, here it matures, the nucleus becomes from round, first bean-shaped, then clawed, and the chromatin structure changes. Various levels of monocyte differentiation were found in peripheral blood, with more mature monocytes predominating in healthy people. In the blood, monocytes are distributed into parietal and circulating pools, exchanging with each other, the quantitative ratios of which may vary. In humans, the circulating pool of Monocytes is normally 18x10 to the 6th degree cells/

kg body weight, and the marginal pool, which currently does not take part in the circulation, adjacent to the inner wall of the microvessel, is 3.5 times larger (63x10 to the 6th degree of cells/ kg body weight). In general, the total pool of peripheral blood monocytes constitutes from 1 to 10% of all leukocytes (80–600 x 109/l). Monocytes circulate in the blood from 36 to 104 hours (1.5 – 4.5 days) and then leave it according to a stochastic principle, interacting with specialized adhesion molecules on endothelial cells. Monocyte migration from the vascular bed to the focus of chronic inflammation occurs through areas of the microcirculatory bed with the second type of endothelium – these are postcapillaries and venules. Once in the focus of chronic inflammation, monocytes migrate. Cell migration is a process of passive displacement of cells or active movement of cellular complexes and isolated cells, caused by complex selective interactions of cellular receptors on the membranes of migrating cells and their microenvironment. Genotypic changes in the Monocyte can occur at different stages of hematopoiesis and the higher, according to the hematopoietic scheme, the greater potency the malignant stem cell will have. Therefore, it is important to know not only what genotypic changes in the nuclear DNA of the Monocyte arose, but also at what level of hematopoiesis they arose, i.e. Not only the nature of genotypic changes (spectrum of disturbances) of nuclear DNA is important, but also the level of genotypic changes (class according to the hematopoiesis scheme). For the “germination”

of a malignant stem cell in solid tumors, the most likely levels of potency are:

1. Class II – pluripotent progenitor cell of the ancestor of myelopoiesis, common to 4 lineages (CFU-GEMMeg) with subsequent development in the direction of the Monocytic lineage.

2. Class III – unipotent progenitor cell of the monocytes (CFU-M). It must be emphasized that genotypic changes in nuclear DNA occur according to a recessive trait, therefore these changes do not manifest themselves in any way in the red bone marrow.

During the process of differentiation, genotypic changes are laid down in the genetic apparatus of the future Monocyte, which morphologically will not differ from a normal bone marrow cell. The acquisition of genotypic changes in nuclear DNA for a Monocyte is not decisive in the possibility of transformation into a malignant stem cell, because it can divide, mature, differentiate, transform into cells of the microenvironment, and transform into a Macrophage. And although irreversible genotypic changes are an absolute necessity for transformation into a malignant stem cell, this is completely insufficient. Genotypic changes in the DNA of the Monocyte nucleus will wait patiently until optimal conditions arise for their manifestation, and then the "nascent" descendants – malignant stem cells – will dominate the host organism.

For the "birth" of a malignant stem cell, subsequent

growth and development of the malignant process, “super conditions” are required, creating an isolated state of the progenitor cell from the influence of the body. These conditions can be called a “pre-tumor” bed in pathologically altered local tissues against the background of pre-tumor diseases of the macroorganism. A “pretumor” bed can be an isolated microcavity, the formation of which during chronic inflammation is a natural process. However, it is not at all necessary that the formed isolated microcavity will become the place where the “birth” of a malignant stem cell will occur. Formation of an isolated microcavity: during the process of inflammation, small blood clots and dead tissue are reabsorbed. Large tissue defects resulting from fibrinous-necrotic inflammation are replaced by scar tissue. Small defects that occur between cells within the stroma first become lumens and then turn into microcavities. In response to tissue damage and under the influence of pathogenetic inflammatory factors, pluripotent poorly differentiated connective tissue cells, called “peripheral blood fibrocytes” or fibroblast-like cells, migrate from the bloodstream. Their immunophenotypic characteristics, combined with the ability to give rise to representatives of fibroplastic cell differential, suggest that they are multipotent mesenchymal stromal cells (MMSCs), constantly circulating in the blood in small quantities. It is these fibroblast-like cells that participate in the formation of the insulating shell of the microcavity, which acts as a “graveyard” for dead

cells. Due to chemotaxis, a certain number of Monocytes enter an isolated microcavity, because not all of them are subsequently transformed into a malignant stem cell, but the transformation process never occurs from single cells. Once in an isolated microcavity, the Monocyte finds itself surrounded by an aggressive oxygen-free environment. He develops structural changes in the cell membrane and chemical changes in the cytoplasm – epigenetic changes. A tissue monocyte appears, which has genotypic and epigenetic changes – this is the potential precursor cell of the primary malignant stem cell of solid tumors. Such a Monocyte remains outwardly normal as long as it is in interphase, but as soon as it begins Mitosis, all changes will become obvious and manifest themselves. It is known that each Monocyte in tissues turns into an organ- and tissue-specific Macrophage during the process of transformation. Transformation is a series of cell divisions during which its phenotypic changes occur sequentially under the influence of the microenvironment. A monocyte, having genotypic and epigenetic changes, attempts to transform into a Macrophage (macrophage blast, promacrophage, tissue macrophage) and begins the process of mitosis, during which a return to the embryonic state occurs. However, after mitosis, the level of genotypic changes appears, as a result of which a block of differentiation of daughter cells occurs and transformation, during which the nature of genotypic changes in nuclear DNA appears. As a result, an unstable active system is “born” –

a malignant stem cell, which has retained many of the basic abilities and capabilities of the mother cell – the tissue Monocyte, which has not completely left the embryonic state and acquires new abilities of its new life: the possibility of uncontrolled division, autonomous regulation, immortality of the population, etc. . A malignant stem cell is a proliferating somatic cell that has a certain level of potency, which corresponds to the level at which genotypic changes occurred in the bone marrow cell during hematopoiesis:

1. If genotypic changes in a bone marrow cell occurred at the level of a pluripotent progenitor cell of the ancestor of myelopoiesis with subsequent development into a monocytic lineage (class II), then the tissue monocyte is transformed into a pluripotent malignant stem cell with pronounced phenotypic heterogeneity and the possibility of the appearance of a "chimera" cell. with multiple differentiation.

2. If genotypic changes in the bone marrow cell occurred at the level of the unipotent progenitor cell of the ancestor of Monocytes (class III), then the tissue Monocyte is transformed into a unipotent malignant stem cell with minimal phenotypic heterogeneity. The "nascent" malignant stem cell, due to proliferation, creates a clone of malignant cells, which are the trigger, regulator and activator of the growth and development of the malignant process.

Thus, the following Monocytes and different groups of cells derived from Monocytes are possible in the human body:

1. The main group is normal Monocytes, which arose from the bone marrow cell and continued on their way into the bloodstream, and then entered the tissues and turned into macrophages.

2. The group of future cancer cells are Monocytes that received genotypic changes in their DNA in the germinal zone, penetrated into the blood, and then into an isolated microcavity in the infected tissue, where they were exposed to the environment. They eventually turned into cancer cells. In the future, contacts are possible between former Monocytes that have turned into Macrophages and former Monocytes that have turned into cancer cells. Most likely, these contacts will not be harmful to cancer cells, because They have the same basis and therefore there is no point in “fighting” among themselves.

3. The group with genotypic changes are Monocytes that received genotypic changes in their DNA in the germinal zone, but did not change phenotypically, although they changed some of their properties. Ultimately, in tissues they turned into macrophages and their derivatives.

MONONUCLEAR ONCOGENESIS PROGRAM

According to the modern theory of molecular genetic mechanisms of multistage carcinogenesis, the "birth" of a malignant cell occurs in three stages: initiation, promotion and progression. The program of the emergence, growth and development of mononuclear oncogenesis in the carrier organism consists of many regular, evolutionarily determined and successively changing periods and stages, separated in time, space and local changes in the cell (nucleus, cell membrane, cytoplasm). Detailed information about the molecular genetic mechanisms of oncogenesis is available in the available literature, so let us summarize and analyze its main provisions. To create the theory of "Mononuclear oncogenesis" as a natural mechanism of the emergence, growth and development of a malignant process, we considered it possible to question the existing theory about the origin of the primary malignant stem cell of solid tumors from cambial cells of the integumentary or glandular epithelium. After all, the question of what cellular and/or tissue substrate the malignant stem cells of solid tumors originate from is still debatable, and the range of cells that could lay claim to the role of the precursor cell of the primary malignant stem cell has not yet been precisely determined.

The first period is the formation of a "pre-tumor" bed.

The first stage:

– is the emergence and development of general diseases of the body, both basic and accompanying: nonspecific changes in tissues of an inflammatory, dystrophic and dishormonal nature; benign tumors; developmental defects; age-related changes, etc.

The second stage:

– is the emergence and development of pre-tumor pathological changes in local tissues: specific morphological, biochemical, immunological and other changes in local tissues in the zone of chronic inflammation. A "pretumor" bed is formed in the form of an isolated microcavity. At the same time, chronic inflammation stimulates hematopoiesis – proliferation of bone marrow mononuclear cells.

The second period is the "birth" of the primary malignant stem cell.

The first stage is initiation:

– in the red bone marrow, as a result of stimulation of hematopoiesis and under carcinogenic influence (ionizing radiation, exo- and endocarcinogens, viruses), a characteristic spectrum of disorders occurs at the gene, chromosomal and genomic levels: amplification (increase in the copy number of genes), deletions, insertions, translocations, micromutations (point substitutions, microdeletions, microinsertions), etc., of a pluripotent progenitor cell of the ancestor of myelopoiesis with subsequent development into a Monocyte lineage (Class II) or

a unipotent progenitor cell of the ancestor of Monocytes (Class III) according to a recessive trait. An initiated cell appears – a mononuclear cell that has genotypic changes in nuclear DNA, but is phenotypically presented as a normal cell – a monocyte.

Initiation conditions:

– the use of the initiator should be one-time and short-term, and the occurrence of mutations depends on the dose of the initiator – the stronger the effect, the more reliable the result;

– initiation occurs only during cell mitosis, i.e. in the zone of natural intensive proliferation of somatic cells;

– initiation is more likely in the area of chronically increased proliferation, stimulated by external or internal influences;

– initiation is irreversible, i.e. mutations that occur at the level of nuclear DNA cannot be restored to normal;

– taking into account that embryonic features appear in a malignant cell, the proliferating zone must begin from the embryonic period of development of the organism, and also during the period of transformation of a normal proliferating somatic cell into a malignant cell, conditions similar to embryonic ones must be created;

– it is known that malignant cells have different levels of potency: from unipotent to pluripotent, that is, the level of activity of the progenitor cell when it transforms into a primary malignant stem cell must be quite high – unipotent or pluripotent;

– initiation must cease completely before the promoter can take effect, i.e. a change in the state of the cell is necessary:

initiation must occur under certain conditions, but further influence (promotion) can be carried out when the cell with an altered genotype is already in other conditions of existence and microenvironment. Thus, a single and short-term carcinogenic effect leads to irreversible genotypic changes in the nuclear DNA of a proliferating somatic cell. However, initiation alone is not enough for the "birth" of a malignant stem cell.

Second stage promotions:

– in an isolated microcavity of a focus of chronic inflammation, an aggressive liquid in an oxygen-free environment affects the cell membrane and cytoplasm of a genotypically altered tissue mononuclear cell. Inside an isolated microcavity under conditions close to embryonic, there is a proliferating cellular composition fixed to the membrane or suspended. Structural changes in the cell membrane occur, with a violation of selective permeability for inorganic ions and "chemical evolution" in the cytoplasm of the genotypically changed Mononuclear cell – epigenetic changes.

Promotion terms:

– promotion is effective only after initiation and, moreover, after the complete cessation of the action of the initiator, i.e. the initiated cell must be in other conditions of existence and microenvironment – in the zone of chronic inflammation;

– the interval between initiation and promotion does not affect the final incidence of malignant neoplasms, i.e. the lifespan of an initiated cell can be different, but it is necessary that it be as

long as possible (months);

– the promoter must influence the initiated cell continuously and for a long time, i.e. an initiated cell with a long life cycle must be in certain isolated conditions (super conditions), in which the aggressive effect on it can continue for a relatively long period (months);

– the promoter can influence the initiated cell in different ways, including the structure of the cell membrane with changes in selective permeability, the chemical state of the cytoplasm, cell differentiation, the possibility of blocking intercellular connections, etc.;

– promotion is reversible at the initial stage, i.e. early manifestations of promoter effects may disappear and the cell will return to its original state;

– genotypic and epigenetic changes in a proliferating somatic cell prepare the mechanism of transformation into a malignant stem cell and simultaneously trigger it. A prerequisite for the implementation of the transformation mechanism is sufficient isolation from the influence of the host organism;

– in an isolated microcavity of chronic inflammation, mitosis of a cancer cell precursor cell occurs, which has genotypic and epigenetic changes, and its transformation into a primary malignant stem cell. During mitosis, the transformation mechanism is realized as a continuous process consisting of two parts: the manifestation of the level of genotypic changes and the manifestation of the nature of genotypic changes;

– at the same time, an unstable active system is "born" – a primary malignant stem cell, which has retained many of the basic abilities and capabilities of the mother cell-precursor of the cancer cell, has not completely left the embryonic state and acquires new abilities in its new life.

Thus, a proliferating somatic cell, having genotypic changes in nuclear DNA, finds itself in "super conditions" of chronic inflammation, where it is exposed to long-term and continuous (months) aggressive influence in an oxygen-free environment. As a result, it acquires epigenetic changes – structural damage to the cell membrane and chemical changes in the cytoplasm. It is currently believed that genotypic and epigenetic changes in a proliferating somatic cell are preparatory and, at the same time, trigger for the mechanism of actual transformation into a malignant stem cell. A prerequisite for the implementation of the transformation mechanism is sufficient isolation from the influence of the host organism.

The third stage is progression (the actual transformation mechanism):

– the formation of a malignant "embryo" due to the proliferation of the primary malignant stem cell – in an isolated microcavity, mitosis of a tissue mononuclear cell occurs, which has genotypic and epigenetic changes and its transformation into a primary malignant stem cell. During mitosis, the transformation mechanism is implemented as a continuous process consisting of two parts:

– part one – manifestation of the level of genotypic changes: the return of the Mononuclear cell during mitosis to the embryonic state and the block of differentiation of daughter cells at the pluripotent or unipotent level, corresponding to the level at which genotypic changes in the nuclear DNA of the bone marrow stem cell occurred during hematopoiesis;

– part two – manifestation of the nature of genotypic changes: the spectrum of changes in nuclear DNA at the gene, chromosomal and genomic levels comes into force: amplification (increasing the copy number of genes), deletions, insertions, translocations, micromutations (point substitutions, microdeletions, microinsertions), etc. An unstable active system "emerges" – a primary malignant stem cell, which has retained many of the basic abilities and capabilities of the mother cell – the tissue mononuclear cell, which has not completely escaped from the embryonic state and acquires new abilities of its new life.

Thus, a proliferating somatic cell, which has primary mutations in the nuclear DNA of the genome as a result of initiation, then structural changes in the cell membrane and chemical changes in the cytoplasm as a result of promotion, turns into a primary malignant stem cell with subsequent progression.

The third period is the growth and development of the malignant process.

Stage first – formation of a malignant "embryo": due to the proliferation of the primary malignant stem cell, the

accumulation of similar or homogeneous malignant cells occurs within the shell of an isolated microcavity. Due to exposure growth, the size of the malignant "embryo" can increase significantly.

Stage second – organization of the primary malignant focus: with the release of malignant cells beyond the isolated microcavity into the intercellular space, subsequent proliferation, appositional and invasive growth, the organization and increase in the volume of the primary malignant focus occurs.

Stage third – organization of a secondary malignant focus – metastasis: invasive growth and angioneogenesis contribute to the penetration of malignant cells into the vascular bed and organization of a secondary malignant focus – metastasis.

The malignant process, as an independent system, is capable of self-organization and self-regulation. Throughout its growth and development, it is accompanied by deliberate death of cells and non-cellular structures, redistribution of water, autonomous regulation, malignant progression, increasing superiority, as well as control and subjugation of the host organism. To create the theory of "Mononuclear oncogenesis" as a natural mechanism of the emergence, growth and development of a malignant process, we considered it possible to question the existing theory about the origin of the primary malignant stem cell of solid tumors from cambial cells of the integumentary or glandular epithelium. After all, the question of what cellular and/or tissue substrate the malignant stem cells of solid tumors originate from is still

debatable, and the range of cells that could lay claim to the role of the precursor cell of the primary malignant stem cell has not yet been precisely determined. Theoretically, any somatic cell can turn into a malignant cell. However, it is impossible to identify transformation processes in vitro and oncogenicity of cells in vivo, because The transformation of a normal cell into a malignant cell is a process initiated at the molecular level.

Important and undeniable statements:

– malignant cells are more similar to each other than normal cells are to each other;

– malignant cells have fewer differences between themselves than the differences between malignant cells and normal cells;

– not a single property that malignant cells possess is possessed by epithelial cells, and not a single function of the epithelium (integumentary, protective, exocrine) is transferred to malignant cells;

– the basic principles of the "birth" of a malignant cell, the growth of the primary focus and the development of the malignant process of various organs and tissues are completely identical.

The question of which cell can lay claim to the role of the progenitor cell of the primary malignant stem cell of solid tumors remains controversial. When analyzing all the cells of the human body, only Mononuclear cells (Monocytes) can claim this role, and there is every reason for this statement, they are:

1. They are somatic proliferating cells.

2. They have a long life cycle (months).

3. They have sufficient autonomy: they are able to move freely throughout the host body through the blood stream, penetrate and migrate in various organs and tissues.

4. They are an intermediate development option in the red bone marrow and bloodstream, and in tissues they are transformed into tissue macrophages.

5. In anaerobic conditions, they can independently switch to the anaerobic type of energy production.

6. They can take on the phenotype of microenvironmental cells – mesenchymal-epithelial transition.

7. They have the ability to influence various vital processes: hematopoiesis, homeostasis, immunity, proliferation, maturation and differentiation of cells, etc. Thus, a mononuclear cell (Monocyte) is a cell that can lay claim to the role of a precursor cell of the primary malignant stem cell of solid tumors.

STEPS

The stages of formation and successive change of generations of malignant stem cells during mononuclear oncogenesis correspond to the stages of formation and successive change of generations of stem cells during embryonic hematopoiesis. The presented comparative analysis of the stages of formation and sequential change of generations of stem cells during embryonic hematopoiesis and Mononuclear oncogenesis shows that Mononuclear oncogenesis is a pathological form of embryonic hematopoiesis in the postnatal period of human development.

Comparative analysis of the stages of formation and change of generations of stem cells during embryonic hematopoiesis and mononuclear oncogenesis.

– The first phase – Mesoblastic, the first generation of stem cells – in the wall of the yolk sac of the embryo, the "birth" of blood stem cells occurs – the first generation.

– The first generation of stem cells – Cytoblastic – in an isolated microcavity formed like the yolk sac of an embryo, the "germination" of a malignant stem cell occurs. Due to proliferation, mass accumulation occurs and the first generation of malignant stem cells is formed. Second phase.

– The second phase – Hepatolienal, second generation of stem cells – blood stem cells emerge from the yolk sac and

populate the liver, which becomes the main organ of embryonic hematopoiesis. The second generation of blood stem cells is formed in it. Liver blood stem cells then colonize the thymus, spleen and lymph nodes.

– The second generation of stem cells Primary-focal – the malignant stem cells exit beyond the isolated micro cavity into the intercellular space and colonize it. Due to proliferation, appositional and invasive growth they organise a primary focus, where the second generation of the malignant stem cells is formed.

– The third phase Medullar (marrow) – the blood stem cells colonize the red bone marrow, where their third generation is formed – this is the final phase of the embryonic haematopoiesis. Medullar (marrow) – the blood stem cells colonize the red bone marrow, where their third generation is formed – this is the final phase of the embryonic haematopoiesis.

– The third and subsequent generations of stem cells Secondary-focal or metastatic – due to the invasive growth and angioneogenesis the malignant stem cells penetrate into the bloodstream and colonize the lymph nodes, the bone marrow, liver, lungs etc., followed by organisation of the secondary malignant focus – mature metastasis, where the third generation of the malignant stem cells is formed. Later, subsequent generations of the malignant stem cells may form.

PROTOTYPES

Mononuclear oncogenesis uses known processes and structural organizations as prototypes, according to the principle "all this was already in the body, only at a different time, in a different place and with other cellular and non-cellular elements." The prototype of the "pretumor" bed, presented as an isolated microcavity, is the structural organization and functioning of the yolk sac of the embryo. In this case, conditions close to embryonic ones arise inside the microcavity, and the "nascent" malignant stem cell conditionally repeats the beginning of embryonic hematopoiesis. The prototype of the structural organization and functioning of the primary malignant focus is the structural organization and functioning of the red bone marrow. In this case, the primary malignant focus is presented as an independent structural unit containing all the classical characteristics of the tissue, possessing autonomy of reproduction and the ability to spread in the host organism. A prototype of the relationships between the structural elements that make up the malignant process and the relationships At the same time, the malignant process is presented as an independent system, which is characterized by its own control over the proliferation, differentiation and maturation of malignant cells, their spread and metastasis, as well as the subordination of vital organs and systems of the host body.The prototype of the

emergence, growth and development of a malignant process is embryonic hematopoiesis. In this case, the malignant process conditionally repeats in a distorted form all the stages of formation and successive changes in generations of stem cells of embryonic hematopoiesis.

BASE

The basis for the growth and development of Mononuclear oncogenesis is a malignant stem cell, and the basis for the "generation" of a malignant stem cell is the return of a tissue Mononuclear cell, which has genotypic and epigenetic changes, to the embryonic state during mitosis, a block of differentiation at the pluripotent or unipotent level and transformation. In the red bone marrow, under carcinogenic effects (ionizing radiation, exo- and endocarcinogens, viruses), a characteristic spectrum of disorders occurs at the gene, chromosomal and genomic levels: amplification (increase in the copy number of genes), deletions, insertions, translocations, micromutations (point substitutions, microdeletions, microinsertions), etc., a pluripotent precursor cell of the ancestor of myelopoiesis with subsequent development into a monocytic germ (class II) or a unipotent precursor cell of the ancestor of Monocytes (class III) according to a recessive trait. As a result, an initiated cell appears in the host organism – a mononuclear cell, which has genotypic changes in nuclear DNA, but is phenotypically presented as a normal cell (Promonocyte, Monocyte). The initiated cell, maintaining the stages of its development in the red bone marrow and vascular bed, enters the focus of chronic inflammation and finally enters an isolated microcavity. Here, surrounded by an aggressive oxygen-free environment, she develops structural changes in

the cell membrane and chemical changes in the cytoplasm – epigenetic changes. A tissue mononuclear cell appears, which has genotypic and epigenetic changes – this is the potential precursor cell of the primary malignant stem cell of solid tumors. Such a mononuclear cell remains outwardly normal as long as it is in interphase, but as soon as it begins mitosis, all changes will become obvious and manifest themselves. It is known that every Promonocyte and Monocyte in tissues turns into an organ- and tissue-specific Macrophage during the process of transformation. Transformation is a series of cell divisions during which its phenotypic changes occur sequentially under the influence of the microenvironment. The promonocyte or Monocyte, having genotypic and epigenetic changes, attempts to transform into a Macrophage and begins the process of mitosis, during which a return to the embryonic state occurs. However, after mitosis, the level of genotypic changes appears, as a result of which a block of differentiation of daughter cells occurs and transformation, during which the nature of genotypic changes in nuclear DNA appears. As a result, an unstable active system is "born" – a malignant stem cell, which has retained many of the basic abilities and capabilities of the mother cell – tissue mononuclear cell (Promonocyte, Monocyte), which has not completely left the embryonic state and acquires new abilities of its new life: the possibility of uncontrolled division, autonomous regulation , immortality of the population, etc. A malignant stem cell is a proliferating somatic cell that has a certain level

of potency, which corresponds to the level at which genotypic changes occurred in the bone marrow cell during hematopoiesis.

1. If genotypic changes in the bone marrow cell occurred at the level of the pluripotent progenitor cell of the ancestor of myelopoiesis with subsequent development into a monocytic lineage (class II), then the tissue mononuclear cell is transformed into a pluripotent malignant stem cell, which has pronounced phenotypic heterogeneity and the possibility of the appearance of a "chimera" cell. with multiple differentiation.

2. If genotypic changes in the bone marrow cell occurred at the level of the unipotent progenitor cell of the ancestor of Monocytes (Class III), then the tissue Mononuclear cell is transformed into a unipotent malignant stem cell with minimal phenotypic heterogeneity.

The "nascent" malignant stem cell, through proliferation, creates a clone of true malignant cells. Under the influence of growth factors secreted by true malignant cells into the intercellular space, "conditionally malignant cells" appear – phenotypically altered integumentary or glandular epithelium. True malignant cells are the trigger, regulator and activator of the growth and development of the malignant process.

MECHANISM

The mechanism of occurrence, growth and development of Mononuclear oncogenesis is a complex process, when each subsequent action is the result of the previous one, each action has its own distinctive features and oncogenesis can end for one reason or another at each of them. Pretumor diseases of the body and pathological changes in local tissues in the zone of chronic inflammation contribute to the formation of an isolated microcavity as a future “pretumor” bed. The microcavity, isolated from the microenvironment, contains an aggressive specific liquid in an oxygen-free environment. Inflammatory mediators initiate an additional requirement for specific tissue immunocompetent cells, therefore hematopoiesis is stimulated and the production of mononuclear cells in the red bone marrow is enhanced, because They do not form a bone marrow reserve. During the accelerated production of bone marrow mononuclear cells and under carcinogenic influence, genotypic changes in the DNA of the nucleus of hematopoietic stem cells occur, with different levels of potency according to a recessive trait. After entering the tissue, mononuclear cells with genotypic changes in nuclear DNA penetrate into an isolated microcavity, where they are exposed to aggressive liquid in an oxygen-free environment – epigenetic changes appear. During the process of mitosis of a mononuclear cell, which has genotypic and epigenetic changes,

a primary malignant stem cell is “born,” which divides to form similar or homogeneous malignant cells and forms a monoclonal malignant “embryo”—a clone of malignant cells within the shell of an isolated microcavity. Subsequent division of malignant cells leads to an increase in their critical mass (number) and is accompanied by an increase in their malignancy (malignant progression), which contributes to the destruction of the shell of the isolated microcavity. The release of malignant cells into the intercellular space and the involvement of the stroma of an organ or tissue in the malignant process means the beginning of the organization of the primary malignant focus. The malignant focus increases in size due to active proliferation, appositional and invasive growth. Active penetration of true malignant cells through tissue barriers (invasive growth), as well as stimulation of the growth of blood vessels (angioneogenesis) contribute to the penetration of malignant cells into the vascular bed and the organization of a secondary malignant focus (metastasis).

FEATURES

A feature of the formation of a “pre-tumor” bed is the obligatory presence of pre-tumor diseases of the body in general and pre-tumor pathological changes in local tissues in particular. In normal healthy tissues, the occurrence of a malignant process is impossible. A feature of preparing a cell for transformation into a malignant cell is the multi-stage process. Moreover, each stage has its own characteristics that determine the possibility of continuing the process, during which decisive genotypic and epigenetic changes can occur. A feature of the “birth” of a primary malignant stem cell is the obligatory entry into the process of mitosis of a cell that has genotypic and epigenetic changes. Only during MITOSIS does the transformation mechanism occur and the level and nature of genotypic changes become manifest. In this case, the transformation mechanism occurs in an isolated microcavity and, thus, escapes the influence and control of local tissues. A feature of the growth of a malignant lesion is its autonomy and ability to self-organize and self-regulate. Using the host organism as the basis for its own development, the malignant process subjugates the normal cellular and non-cellular structures of vital organs and systems. A peculiarity of the mechanism of penetration of mononuclear cells from the vascular bed into the tissue, and of malignant cells from the primary focus into the vascular

bed, is the use of the same section of the microvasculature – the postcapillary and venule. Figuratively speaking, “through whatever “doors” the cells came out, through the same ones they returned.” A feature of the development of the malignant process is the perverted repetition of embryonic hematopoiesis. The host organism unconsciously “connects” a false option to enhance its ability to survive by maintaining individual aging organs. In reality, this path is a dead end, and the mechanism is destructive.

RESULT

As a result of pretumor diseases of the body in general and pathological changes in local tissues in particular, an isolated microcavity is formed as a “pretumor” bed. However, pre-tumor changes in local tissues are only the necessary preparation for creating conditions under which a genotypically and epigenetically altered cell can transform into a malignant stem cell. In the red bone marrow, as a result of carcinogenic effects, various genotypic changes occur in the DNA of the nucleus of the pluripotent progenitor cell of the ancestor of myelopoiesis with further development into a monocytic germ or unipotent progenitor cell of the ancestor of Monocytes according to a recessive trait. These changes do not lead to disruption of cell differentiation, but are inherited by more mature cells – Promonocyte and Monocyte. As a result, an initiated cell appears – a genotypically altered mononuclear cell. In an isolated microcavity of a focus of chronic inflammation, initiated cells are exposed to aggressive fluid in an oxygen-free environment. This leads to structural changes in the cell membrane with disruption of its selective permeability and “chemical evolution” in the cell cytoplasm. As a result, epigenetic changes appear in the genotypically altered Mononuclear Cell. As a result of mitosis of a genotypically and epigenetically altered mononuclear cell, the actual transformation mechanism

is launched and the primary malignant stem cell is “born,” which divides to form a clone of the same type or homogeneous malignant cells. As a result, a malignant “embryo” is formed – a clone of malignant cells within the shell of an isolated microcavity. The result of malignant cells leaving the shell of the isolated microcavity and involving the stroma of the microenvironment in the malignant process is the organization of a primary malignant focus. The increase in volume is the result of active proliferation, appositional and invasive growth of malignant cells, and penetration into surrounding tissues is the result of invasive growth of true malignant cells. As a result of the active penetration of true malignant cells through tissue barriers (invasive growth), as well as stimulation of the growth of blood vessels (angioneogenesis), malignant cells penetrate into the vascular bed and participate in the organization of a secondary malignant focus (metastasis). As a result of the ability to independently control the proliferation, differentiation and maturation of malignant cells, the spread of malignant cells throughout the host body and the organization of metastases, as well as as a result of the influence on the vital organs and systems of the host body with their subsequent subjugation, the malignant process develops as an independent system.

FUNDAMENTALS

Statement 1: The precursor cell of the primary malignant stem cell of solid tumors is a tissue mononuclear cell (Promonocyte, Monocyte), which has genotypic and epigenetic changes.

Statement 2: The basis for the "generation" of a malignant stem cell is the return of a tissue mononuclear cell, which has genotypic and epigenetic changes, to the embryonic state during mitosis, a block of differentiation at the pluripotent or unipotent level and transformation.

Statement 3: The mechanism of "generation" of a malignant stem cell is a complex multi-stage process, when genotypic changes in a bone marrow mononuclear cell under carcinogenic influence sequentially appear, epigenetic changes in the same but tissue mononuclear cell under the influence of "super conditions" of an isolated microcavity, and mitosis is the starting point for their implementation.

Statement 4: The polymorphism of malignant cells is due to the variety of options for their "nucleation", maturation and differentiation, as well as their own evolution and the influence of the microenvironment.

Statement 5: A malignant focus is an independent structural and functional formation that has characteristic features and conditionally repeats the structural organization and functioning

of the red bone marrow.

Statement 6: The stages of formation and successive change of generations of malignant stem cells conditionally repeat the stages of formation and successive change of generations of stem cells of embryonic hematopoiesis.

Statement 7: The malignant process, as an independent system, is capable of self-organization and self-regulation; many evolutionarily determined mechanisms lie in its occurrence and development.

CONCLUSIONS

Based on the above, the following conclusions can be drawn:

1. The precursor cell of the primary malignant stem cell of solid tumors is a tissue mononuclear cell (Monocyte), which has genotypic and epigenetic changes.

2. The primary mutation of the nuclear DNA of the Monocyte genome occurs in the red bone marrow after the carcinogenic effects of the initiator (ionizing radiation, endo- and exocarcinogens).

3. From the red bone marrow, the monocyte enters the bloodstream, where it remains from 36 to 104 hours (1.5 – 4.5 days), and then leaves it according to a stochastic principle, migrating to the focus of chronic inflammation.

4. The primary mutation of the nuclear DNA of the Monocyte genome can be determined using sequencing, after isolating the Monocyte from the circulating blood of a person with a solid malignant tumor.

5. Knowing the primary mutation of the nuclear DNA of the Monocyte genome, as a precursor cell of a cancer cell, it is possible to create a therapeutic anti-cancer DNA vaccine “on demand”.

6. The basis for the “generation” of a malignant stem cell is the return of a tissue mononuclear cell, which has genotypic and epigenetic changes, to the embryonic state during mitosis,

a differentiation block at the pluripotent or unipotent level and transformation.

7. The mechanism of "generation" of a malignant stem cell is a complex multi-stage process, when mutations in the nuclear DNA of a bone marrow mononuclear cell successively appear under carcinogenic influence and epigenetic changes in the same, but tissue mononuclear cell under the influence of "super conditions" of an isolated microcavity, and mitosis is the starting point for their implementation.

8. Initially, this will be an "on demand" vaccine, then it is possible to use a vaccine based on a set of primary mutations in the nuclear DNA of the genome of the progenitor cell of the cancer cell.

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