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The Roots and Mechanisms of Oncology

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Abstract

The theory of somatic mutations is incorrect, and the concept of "mutation" is incorrectly used. Etiological classification of tumors: 1) Tumors of malignant proliferation. Tumor cells are not specific. Tumor growth of malignant proliferation is provided by the reproduction of normal cells. The trigger mechanism of division is the interrelated actions of all the constituent parts of the tissue. The tumor mass increases due to the division of normal cells during its stimulation and dysfunction of its inhibitors and due to the predominance of cell proliferation over apoptosis. Calcium contributes to the formation of an independent structure. A tumor is a hierarchical system of its tissue and distant parts (metastases) that carry out the mutual influence. 2) Transgenic (infectious) tumors – a hybrid of a somatic cell and a microbe. They may be contagious. 3) Gestational tumors. 4) Tumors of genetic aberrations.

Keywords: classification of tumors, malignant proliferation, transgenic tumors, gestational tumors.

1. Introduction

A large number of theories have been put forward to explain the etiology of tumors (Ermolenko, 2012). Now two ideas are being discussed in science. At the beginning of the 20th century, (Boveri, 1914) put forward the idea of DNA mutations, trying to explain carcinogenesis. The idea turned out to be a viable organism. The real criticism pointing to its flaws was not paid attention, at the same time it explained many properties of carcinogenesis and won the trust of many researchers. At present, the idea is called the theory of somatic mutations (SMT) and occupies a leading position in world science. In the past 20 years, its position has become precarious due to the fact that this theory is confronted with a low level of therapeutic results (Godlee, 2016) and a discrepancy between scientific data and theory (Brinster, 1974; Mintz, Illmensee, 1975). In parallel with SMT, less intensively, the tissue theory of carcinogenesis was developed, in which it was suggested that carcinogenesis occurs not at the cellular but at the tissue level of biological organization. This approach is clearly consistent with extracellular theory, according to which a cell is completely dependent on the extracellular matrix (Ermolenko, Perepada, 2007).

The tissue theory of carcinogenesis was first proposed by C.H.Waddington (Waddington, 1935). N. N. Petrov (Petrov, 1958) found SMT errors, other researchers (Hodges, 1977) supported the idea of Waddington. In the future, this idea continued to develop (Cherezov, 1997; Sonnenschein, Soto, 1999). Recently, this theory has gained wide support from researchers (Ermolenko, 2012; Sarode et al., 2016). However, the supporters of SMT use it as a tool to explain many of the phenomena of cancer and do not plan to give up their beliefs. They propose to consider these two theories, explaining the mechanisms of carcinogenesis, as independent and compatible.

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Such an approach is consistent with integrative views, and it is considered that they have a higher value than the two theories taken separately. In my opinion, in order to defeat oncology, the Rubicon must be crossed — it is necessary to abandon SMT once and for all.

I intend to identify misses of the main provisions of modern oncology and give a new interpretation of the nature of tumors, their classification, stages and mechanisms.

2. Discussion

Classification of tumors

Oncologists use the generally accepted informative international classification indicating the exact nomenclature. However, today there is no etiological scientifically based classification of oncological diseases, so I created an etiological classification of tumors:

Root №1. Tumors of malignant proliferation.

Tumor cells do not exist in reality. The cells in the tumor are materially identical to other normal cells (Petrov, 1958). The tumor mass increases due to the division of normal cells during its stimulation and dysfunction of its inhibitors and due to the predominance of cell proliferation over apoptosis (Repina, 2004). A special place in this type of oncology is occupied by the tumors of hormone-producing organs, whose growth occurs due to the violation of the interaction between stimulating organs and target tissues.

Root №2. Transgenic (infectious) tumors are a hybrid of a somatic cell and a microbe.

There is an impressive amount of scientific publications on horizontal gene transfer (Syvanen, 1994). These data suggest that it is possible to combine the genetic material of micro- and macroorganisms. The virogenetic hypothesis suggests that viruses transform a cell into a tumor cell. Some researchers suggest that the hybrid is identical to other tumors. I am convinced that the newly formed separate organism (hybrid) has new properties. Its life is determined by a number of factors: the influence of the surrounding microorganisms; the functioning of the immune system of the macroorganism; absence of division inhibitors; the state of the extracellular matrix of tissue; carcinogens disorganize the tissue, thus may contribute to the formation of a hybrid.

Root №3 Gestational tumors include tumors of dysembryogenesis, as well as germ cell tumors, trophoblastic and coelomic epithelium tumors.. Enchondromatosis is a hereditary disorder of bone enchondral development. With such a disorder, chondrosarcomas often develop. The remains of the fetal chord are the source material of the chordoma. The parasitic twin (ischiopagus) shows itself either as separate organs or as highly differentiated tissues (for example, hair, muscle, bone tissue, a detached eye with the unusual localization for them; a germ in the intestine or in the lung). Oncologists call this phenomenon teratoma. These formations have similarities – well-differentiated tissues, but the origin of parasitic twins can be different: disturbances in the development of the embryoblast or the formation is due to the disembryogenesis of primary germ cells. There is the assumption unproved by the science that identical twins develop from the first two blastomeres. It is more logical to assume that they develop from the inner cell mass. My judgment is confirmed by the fact that the armadillo (*Dasypodidae*) naturally produces four identical twins due to the division of the embryoblast (Carlson, 1983). With its proper division, normal twins develop, and with incomplete separation – Siamese twins are formed, facultative tissues and organs – the ishiopag (ischiopagus). With minor failures, hamartomas are formed. These neoplasms are considered to be tumors. Some variants of the syndrome of MEN are believed to be the result of neural crest disambiogenesis, the cells of which are capable of migration and intensive diffusion (Pinsky, Beloborodov, 1999).

Germ cell tumors are caused by abnormal development, as well as by the associated with it disruption of primordial germ cells migration during ontogenesis. At the same time localization affects their morphology. Initially in multicellular organisms the germ cells were located in an organ which during phylogenesis is transformed into the primary intestine. Later becomes natural the migration of the primary germ cells from the outgrowth of the intestine, called the yolk sac (saccus vitellinus) to the place of permanent residence – in the gonads (Carlson, 1983). The symmetrical organ for the gonads is the lungs (Ermolenko, Perepada, 2007). In the process of embryo development, the primary germ cells sometimes migrate to phylogenetically related places — the intestines and lungs. Due to the impaired induction, the development of the primary germ cells is distorted, they slow down in the development. They can migrate to the mediastinum, brain and other parts of the body (Willis, 1962).

It is known that these tumors, regardless of their nature, are characterized by the presence of the 12p[i(12p)] isochromosome without a long arm, and with a short arm duplication (Schmoll, 2002). The NANOG and OCT 3/4 genes reflect polypotency and serve as accurate indicators of the malignancy of germinative cells (Medvedev, 2008). Consequently, there are genes that determine the development of germ cell tumors.

Distorted cells of the trophoblast and coelomic epithelium can be further expressed as tumors (Karseladze, 2000).

"Branchiogenic tumors", interdigital membranes, additional fingers of the hands are the result of a deviation in embryogenesis. Such deformities are difficult to attribute to oncology.

Root №4. Tumors of genetic abnormalities.

In scientific publications about 1000 types of gene abnormalities are described which are the cause of many hereditary biochemical disorders (Vasiliev, 2006). There is documented evidence that defects in DNA recovery genes can lead to hereditary syndromes of premature aging, oncology of many organs (Lombard. et al., 2005).

The chromosomal abnormality found in myeloblastic leukemia is caused by the “Philadelphia chromosome”. It is known that aberrations in the gene CHEK2 (Li-Fraumeni syndrome) increase the likelihood of developing oncology of the mammary, prostate, colon (Cybulski et al., 2011). REQL4 gene aberrations are shown by bone tumors, as well as Rothmund – Thomson syndrome. Due to the dysfunction of the RB1 gene, a congenital form of retinoblastoma develops. Due to the breakdown of EXT genes with tumor suppressor function, chondrosarcomas can develop (Hecht et al., 1997). Hereditary multiple endocrine neoplasia (MEN) is also known. Some variants of the syndrome of MEN are believed to be genetically determined (Caldas, Ponder, 1997). I did not set myself the goal of reviewing scientific reports on the relationship of chromosomal changes and hereditary human cancers. More detailed scientific publications on this topic can be found in broad reviews, in particular from E.N. Imianitov and R.P. Hanson (Imianitov, Hanson, 2004).

The staging of malignant fission tumors.

Tumor development is usually divided into two stages – initiation and promotion. In the initiation stage, there are several substages. In the second stage (promotion) the final substage – progression – is identified. The proposed division of carcinogenesis is derived from clinical observations. This interpretation does not explain the processes occurring in the structure of the tissue, and does not reflect the essence of the phenomenon. I also believe that the formation of a tumor has two stages, but they do not have additional gradations. The processes occurring in the structure of tissue are radically different from each other. Initially, there are hidden conditions that contribute to the occurrence of a tumor. This stage ends with the formation of a tumor germ. The promotion stage is characterized by the expansion of the tumor, the uniformity of events, the progressiveness of the process acceleration, therefore, it is clinically shown in different ways.

Mechanisms of development of malignant fission tumors.

There are several mechanisms for the formation of malignant tumors.

I. One of them is due to the disorganization of the tissue, which is explained by the following factors:

a) As a result of slowing down the excretion of products of cellular metabolism, changes in tissue homeostasis occur, and then tissue dysfunction. Slowing the export of cell metabolism products increases the size of cells and the intercellular space, leading to compaction of cells, interfering with the functioning of the tissue. Under stress, autophagy and sisterhood levels decrease and TOR (Target of Rapamycin) production increases. An increase in the total number of aging cells reduces the proportion of stem cells, thereby stimulating division, leading to the onset of carcinogenesis. In conditions when dividing cells interact with healthy cells and extracellular structures, the process develops slowly. When the stimulation of cell division coincides with the decrease of the function of factors inhibiting the proliferation, the expression of carcinogenesis begins.

b) The aging of the organism is due to the genetically programmed process of cell life. As a result, the quantity and quality of proteins is disturbed, the structure of collagen of the connective tissue is distorted. The local influence on the tissue of radiation, toxic chemicals, aggressive microorganisms causes local aging.

c) The accumulation of substances peroxidation in the body deteriorates the properties of membranes, which leads to disruption of the transport of ions, primarily protons and ionized

calcium. Active forms of oxygen damage not only the membranes, but also DNA, nucleotide coenzymes, radically change the cell metabolism and the entire tissue architecture.

d) Toxic substances penetrate the extracellular medium, causing pronounced distortions in the production of protein in cells, differentiation of connective tissue, and thus disrupt the structure of the tissue.

e) The immunopathological process is shown in the form of autoimmune inflammation due to the reaction of antibodies and T-cells with its own tissues, and as the final – damage and destruction of normal tissues. Autoimmune carcinogenesis develops due to necrosis of its own tissues. Immunopathological process that disrupts tissue organization is also expressed as an allergy, in which inflammatory humoral and cellular modulators enter the pathological zone, causing exudation, cell emigration, proliferation, increase of vascular wall permeability, increase of chemotaxis of microorganisms, and potentiate the development of edema in the site, increase emigration there leukocytes and microorganisms.

f) Diseases of the deposits in soft tissues (hyaline, amyloid, pigments, urates, purines, calcium, iron) change the structure of organs, disrupting their trophism and metabolism: the result of progressive amyloidosis is atrophy and necrosis; The abnormal exchange of stable complexes of nucleic acids with proteins leads to disintegration into the original constituents, even up to uric acid, which can accumulate in soft tissues and tendons and cause necrosis around which inflammatory infiltration develops with the presence of "giant multicore cells". If there is an impairment of phosphorus and calcium metabolism, calcium phosphate can be deposited in tissues with the formation of macrophage granulomas. The number of pigments can be increased by deposition in soft tissues in the form of nevi and jaundice. With all the variety of substrates that accumulate in organs, a common characteristic is their ability to change metabolism and trophism of tissues and influence the proliferation.

g) Medical statistics show that patients with diabetes mellitus are much more likely than the general population to suffer from oncology. At the same time, a higher risk of developing oncoprocess is only for some localizations – pancreatic and liver cancer is most often detected (Bowker et al., 2006). Ways of the formation of malignant tumors in diabetes are varied: tissue structure disorders; disruption of the insulin receptors and the associated stimulation of insulin secretion; pathological metabolism; genetic aberrations. In diabetes, dystrophic processes slowly develop, disrupting the organization of the pancreas and then other internal organs. In the pancreas there is an accumulation of amyloid until it completely replaces the islets of Langerhans which can be replaced by non-functional connective tissue. Diabetes mellitus is characterized by increased plasma osmolarity due to hyperglycemia, which causes dehydration of cells throughout the body and, as a result, hypoxia. Hypoxia is aggravated by microangiopathy of the microcirculatory bed, resulting from the addition of sorbitol and fructose and other metabolic products characteristic of diabetes mellitus. In the non-enzymatic reaction of glucose with proteins, foreign substances with antigenic properties are formed, causing autoimmune damage and tissue ischemia. The end result of such reactions is necrosis, which is a precursor of oncology. Glucose is the main energy substrate of life processes. When insulin deficiency or resistance to it, the flow of glucose into the cells decreases and its content in the blood increases. This stimulates the production of insulin and glucose. This is the way to stimulate the proliferation of interested organs.

The beginning of type 2 diabetes mellitus is often accompanied by chronic hyperinsulinemia, which is also associated with long-term insulin therapy which contributes to the development of tumors. With hyperinsulinemia, the tumor process is more severe, postoperative complications occur, survival decreases and cancer mortality increases (Bowker et al., 2006). Its trigger is the activation of the mTOR signaling pathway. As a result, inhibitors of apoptosis and factors of angiogenesis increase, cell growth and proliferation is accelerated, and a tumor is generally formed. Moreover, studies have shown that the risk of developing liver and pancreatic cancer associated with the stimulation of their work is the highest. Some researchers estimate pathological metabolism as an independent factor of increased cancer risk. Hyperestrogenia, characteristic of patients with an increased accumulation of adipose tissue, is a leading mechanism aimed at increasing the incidence of cancer (Cleary, Grossmann, 2009). The authors point to the effect of aberration of genes associated with insulin production and sensitivity to it on the risk of tumors.

h) Chronic trauma.

The significance of acute tissue damage for oncology has not been proven, but there is much evidence of the involvement of chronic trauma in the development of tumors. It is known that permanent thermal trauma causes oncology (kangri burncarcinoma) (Chaklin, 1963). Statistics show that cholelithiasis is accompanied by cancer of the gallbladder (Darawish, 2006), and a prolonged mechanical effect of stones on the gallbladder mucosa is assumed. There is also a similar connection between the occurrence of tumors in the oral mucosa in chronic trauma to it by its defective teeth or their substitutes (Bulyakov, 2005). It can be assumed that prolonged use of excessively hot food can have the same effect. It is believed that not only mechanical and thermal, but also ultraviolet, X-ray and radioactive radiation can cause oncology. This also applies to chronic chemical and infectious agents that cause inflammation (Podilchak, 1965). It should be noted that chemical and infectious effects, like chronic stimuli, are not associated with DNA changes. Trauma changes the structure of the tissue and the interaction of the epithelium and stroma. The result is tissue proliferation in response to the damage. R. Virchow attached great importance to chronic inflammation in carcinogenesis.

II. Cancer, which is based on the mechanisms of hormonal imbalance.

The function of hormone glands is balanced by stimulation and inhibition of hormone producing cells using negative feedback. The number of metabolic products of hormones in target cells regulates their synthesis, directly affecting the glands themselves, as well as through the hypothalamus. The production of tropic hormones is regulated by the hormonal level of the glands themselves. Distorted metabolism contributes to the formation of defective hormones, thereby destroying the feedback and the entire balancing mechanism. As a result, hormone-producing cells are stimulated. The mechanisms of interaction of glands and target tissues using feedback work in the regulation of the functions of the gonads, adrenal glands, thyroid gland.

III. Cancer formation, which is based on the mechanisms of interstitial imbalance.

Chronic infection creates conditions for prolonged stimulation of the immune system and leukopoiesis, and in combination with the non-functionality of the fission inhibitors can be a trigger for carcinogenesis of the lymphatic system. It can be assumed that some antibiotics and carcinogens can react with fission inhibitors, inactivating their function.

Available scientific publications on oncology do not give reasonable ideas about the nature of carcinogenesis. Scientists and oncologists practically do not use basic research in biology, physics, biochemistry — studies of the development of the organism and the life of the cell, induction and field effects, and information intercellular interactions. SMT does not provide a clear understanding of the term "mutation": deviations in the structure of DNA (genetic aberrations) and regular changes in DNA that ensure the functioning of cells are considered as mutations. The medical encyclopedia gives a specific definition: “mutation is a permanent change in the properties of a cell or organism that can be inherited by the descendants of a given cell or organism, mutations do not have a reverse development” (Great medical encyclopedia. Ed. Acad. B.V. Petrovsky, 1981). Due to mutations, the evolutionary process developed and new classes of animals were formed. The experiments of R.L. Brinster (Brinster, 1974) with enucleated mouse egg show the absence of mutations in oncology, the “tumor” characteristics are not transmitted to the daughter cells. These findings have been confirmed by other researchers (Mintz, Illmensee, 1975), (Li et al., 2003). I.N. Shvemberger (Shvemberger, 1987) showed that tumor cells are able to regress. And modern studies also claim that tumor processes are reversible (Telerman, Amson, 2009).

Chemical compounds in DNA are deterministic and complementary, but SMT claims that many chemicals can react with it, causing cell division. The cell cycle of division has been studied thoroughly, and there are no mechanisms for the influence on it of the "carcinogens" (Nurse, 2002). According to SMT (including the theory of somatic mosaicism), various carcinogens produce DNA mutations in a limited cell volume, they trigger spontaneous, irrepressible division of cells and their descendants.

It is known that the "carcinogens" in most cases are inert. However, according to the judgment of SMT supporters, after metabolic transformations, they are able to react with nucleic acids. However, xenobiotics are able to penetrate the cell and react with DNA (Biochemistry ed. by E.S. Severin, 2003), besides, as a result of random replication failures, nucleotide deamination disorders, depurination, DNA structure changes occur. These processes occur regularly, but since the multilevel system of DNA structure repair works, the process is normalized. Otherwise, the cell

may inadequately function or die, but the division cycle does not start in the damaged cell. SMT claims that countless chemical and physical factors trigger carcinogenesis, and on this basis it is concluded that it is poly-etiologic. Since, according to this theory, genetic mutations are the only way to form a tumor, this is the theory of mono-etiologic carcinogenesis. The SMT claims that radiation causes certain changes that cause the cell to divide. The idea of chemical carcinogenesis is logical, but unfounded, and radiation carcinogenesis is complete absurdity. X-rays and radiation have a random damaging effect on matter, and SMT ascribes to them creative properties – creation of a tumor. Practice shows that the incidence of oncology is correlated with the prevalence of the use of certain chemicals and radiation, which led to the conclusion that these factors cause cancer. However, it can be assumed that they are not the cause of cancer, but only participate in cancer development.

The clonal-selective idea of carcinogenesis states that random DNA changes in a single cell or in a limited number of them can transform them into a clone of cells with high genetic variability, and then, by natural selection, more and more autonomous and aggressive subclones survive and accumulate (Bachtin et al., 1987). Such a conclusion is not justified, since natural selection extracts only viable organisms and does not create new species (Vorontsov, 1984). It can be assumed that at the cellular level there are no mechanisms for creating specialized cells with separate characteristics. Infectious agents, being one of the mechanisms of carcinogenesis, are capable of disrupting the structure of the tissue (see paragraph “h” of this article). This type of oncology is usually not considered to be a transmitted disease. By its very nature, SMT does not suggest the possibility of transmitting cancer from one individual to another, however, there is a transmissible oncology: in dogs, the venereal sarcoma (the canine transmissible venereal tumour – CTVT); facial tumors (Devil facial tumor disease – DFTD) of Tasmanian devils (*Sarcophilus harrisii*); Syrian hamster tumors (*Mesocricetus auratus*), as well as disseminated neoplasia in marine bivalve mollusks (*Mya arenaria*). Infection occurs through the transmission of live "cancer cells"A.A. (Bostanci, 2005), according to our classification these are transgenic tumors.

The SMT paradigm is that intranuclear processes trigger carcinogenesis. It is known that the cell and its components do not live by themselves, but closely interact with the extracellular matrix, are susceptible to the induction effects of the stroma of the tissue, are in a system of certain intercellular mechanisms similar to the interaction in microbial populations (cell sensing systems (CSS) (Oleskin, 1963). Moreover, the initiation of carcinogenesis is considered to be a chain of spontaneous reactions. In fact, carcinogenesis is a natural process caused by the functioning of tissues. The chemical components determine the course of the reaction. The presence or absence of any substances leads to certain interrelations, reactions of components. The tumor tissue in its chemical composition is not different from normal tissues, but it is not normal, since its function is not coordinated with the vital activity of the surrounding tissues and the whole organism. The imbalance of substances, although characteristic of normal tissue, determines impaired function. SMT does not allow the probability of hierarchy of the tumor process, when induction and informational interaction of tissues can contribute to the separation of a part of the tissue into an independent structure. This theory does not explain the formation of independent growth centers after the elimination or disintegration of the central part of the tumor. Tumors can occur simultaneously and sequentially in different tissues under appropriate conditions.

Modern oncology theory suggests that the immune system is able to recognize and kill "tumor cells." In fact, natural immunity has no mechanisms for performing such a function, it is not able to distinguish tumor cells from other normal cells, to reveal “mutated” DNA. On the contrary, its negative role in carcinogenesis is proven. The autoimmune process causes fibrinoid necrosis due to the fact that autoantibodies bind to the components of tissues (Potekhin, Malyshev, 2000), and cell death enhances proliferation. In the compromised tissue, the chalons function inadequately, which also enhances the malignant proliferation. The role of immunity in oncology is very large – it is able to eliminate infectious tumors, and induced immunity makes a priority in the therapeutic process of oncology.

3. Conclusion

It is known from embryology experiments that the upper lip of the blastopore and then the chord determine the differentiation and division of the cells of the developing organism. From this fact, it is possible to make a reasonable conclusion that there is a non-chemical effect of tissues on the mitotic process. A.G. Gurwitsch (Gurwitsch, 1922) introduced the concept of a morphogenetic

field and mitogenetic radiation into the science. C.Sonnenschein (Sonnenschein, Soto, 1999) broadened the idea and suggests that disruption of the interaction of tissues can lead to mitotic cell activity and tumor development. However, the existence of tissue fields has only been proven indirectly, there is no information about their parameters, confirmed by devices, therefore, there is no evidence of the formation of a tumor due to morphogenetic fields. This theory does not take into account other (ultrasound, ultraviolet, electromagnetic) interactions. In modern ideas the leading importance is given to the nature of tumors and extracellular structures (De Clerck et al., 2017).

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