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The Trigger of Oncology

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ABSTRACT

Proposed own view of the nature and etiological classification of tumors. The article makes a number of conclusions. "Tumor cells" do not exist in nature. The tumor develops due to the malignant dividing normal cells. Carcinogens do not cause tumors, and are part of the mechanism of tumor formation. The immune system is unable to distinguish cells of tumors of malignant proliferation and congenital tumors from other normal cells of the body. The immune system can play a key role in the tumor formation in case of autoimmune diseases. But it can slow down or even eliminate the tumor process caused by transgenic organisms. Tumors derived from transgenic microorganisms can be contagious as other infections. Induced immunity makes a significant contribution to the treatment of tumors. Disorder in the removal of the cells production is a part of the mechanism of malignant proliferation. The mechanism of malignant proliferation is not triggered by mutations in chromosomes in a single cell or in the "tumor field", but by the interrelated actions of all cells and extracellular matrix substances involved in the process, and is caused by an imbalance of stimulants and inhibitors of cell division and is accompanied by a predominance of cell proliferation over apoptosis with the modified architectonics of the cytoskeleton and the extracellular matrix.

Calcium initiates the formation of extracellular matrix – a framework of self-structure. Tumor a hierarchical system of all cells and tissues of the tumor and its metastases causing interference.

Keywords: Classification of tumors, Malignant proliferation, Transgenic tumors, Gestational tumors

INTRODUCTION

Etiology and pathogenesis of the tumor diseases, in spite of the great efforts in the study of their reasons and peculiarities, are in the range of the most complicated issues of modern medicine. There suggested many theories for the explanation of the tumors etiology [1].

The leading theory of carcinogenesis is mutational genetic. According to this theory, any factors (physical, chemical, biological), influencing the cell genetic apparatus, transform normal cells into tumor ones. This hypothesis does not explain the phenomenon of a common denominator, when carcinogenic factors are different, and the result is the same, i.e., cell malignization. When explaining the carcinogenesis mechanisms, scientists make incorrect conclusions. Is it possible to assume the source of ionizing radiation, which is purely destructive, suddenly becomes creative and produces a new form of life? Ionizing radiation causes accidental damages. They cannot produce a targeted influence on certain genes that provoke changes in chromosomes, leading to cell division. The transformation of normal cells into tumor ones is a rather complex process, which is difficult to accept as a casual event. Changes occur simultaneously in strictly defined loci and not in one gene, but in several. The purpose of this work is to criticize the main ideas of oncology and to present to you my one opinion on the tumor nature.

TUMOR CLASSIFICATION

A unified presentation of clinical and pathomorphologic data allows oncologists of different countries to describe and evaluate similar tumors in a similar way. The international classification of oncological diseases (IDC-O-2) published by the WHO in 1990 is a fundamental document in this area [2]. The tumor-related information allows drawing a conclusion there is no etiological, scientifically justified classification, and without knowing the nature of tumors, reasonable treatment is impossible. The identification of the etiological factors of human tumors is the necessary prerequisite for their prevention.

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In my opinion, tumors are divided into four types: tumors of malignant proliferation, transgenic tumors, gestational tumors and tumors genetic aberrations.

The tumors of malignant proliferation

Malignant proliferation is a process in which normal cells have to divide continuously as a result of two factors at work in the same time – continuous division stimulation and absence of division inhibition. In this category, we have hormone-dependent tumors caused by failures in the feedback between stimulating organs and target tissues.

According to the popular gene mutation theory of tumor etiology, it is gene mutations that take place when the cell is exposed to carcinogenic factors that cause oncological diseases [3-5]. These mutations transform normal cells into "tumor cells" with rapid uncontrolled proliferation. This hypothesis is hardly correct as tumors quite often regress [6-10] and the nucleus of a tumor cell when transplanted into a normal enucleated oocyte would behave normally [11]. Encyclopedic information: "a mutation is the permanent alteration of the cell properties or an organism, which can be inherited by the descendants of the given cell or the organism" [12]. The extracellular theory [13] holds that the behavior of cells (division, stable functioning, aging and death) are determined not by gene mutations but changes in the tissue structure – composition of the cellular membrane, extracellular materials, tissue stroma induced changes, cell sensing systems (CSS) similar to quorum sensing systems (QSS) of microorganisms.

In my view, tumors of malignant proliferation start growing when normal cell proliferation is stimulated while the inhibition of the process is impaired either as a result of changes in the inhibitors or the loss of the ability of the cells to interact with them. Both mechanisms are a result of changes in the composition and structure of cells and tissues with subsequent changes in the functions of the cells and extracellular matrix. These changes can be caused by certain interrelated factors such as slower clearance of substances from tissues, slower autophagia, accumulation of carcinogens that can interact with extracellular matrix and form insoluble compounds. A mismatch of cellular division stimulation and inhibition leads to uncontrolled proliferation of normal cells.

In my opinion, the reason of the tumors of the malignant proliferation is the stimulation of the division under functionality of the inhibitors of the division, which can be a result of the production of the distorted inhibitors, and also because of the inability of the cell to come into contact with the inhibitors. Both mechanisms are stipulated by the changes of the composition and the structure of the cells and tissue that entails the changes of the cells and extracellular matrix functions. These changes arise under the influence of a number of the interconnected factors: the decelerated removal of the substances from the tissues, the autophagy deceleration, accumulation of the carcinogens, which provide the insoluble compounds with the extracellular matrix structures. In the situation when the cells have the stimuli for the division and the effect of the inhibitors' influence is slowed down, the unrestrained proliferation of the normal cells comes. There is the evidence the extracellular matrix may initiate carcinogenesis [14] through the infiltration of altered tissue by means of monocytes. Together with them, T-lymphocytes migrate and accumulate, and then an extracellular matrix including I and III type collagen, proteoglycans, elastin is formed. The flow of calcium into the intercellular space is associated with the formation of soluble complexes of calcium ions plus amino acids, glycosaminoglycans of the basic substance, collagen and elastic fibers of connective tissue. Calcium ions are integral components of many biostructures and evolutionarily ancient mediators, and they regulate many metabolic processes and physiological functions. It is calcium that initiates the formation of the extracellular matrix, i.e., the basis of an independent structure. If cells have stimuli for division and the action of its inhibitors is blocked, uncontrolled proliferation of initially normal cells occurs.

Substances that stimulate cell division are synthesized by the cells and act within the cells [4]. Those found in the cell microenvironment interact with the cell surface [15,16]. The proliferation of different cell types is determined by a totality of growth factors rather than just one of them. A big group of growth factors is represented by cytokines (interleukins, tumor necrosis factors (TNF), colony-stimulating factors (CSF) and others). All cytokines are polyfunctional; they can both enhance and inhibit proliferative reactions. In normal eukaryotic cells, the cellular cycle is regulated by alternating activation/inhibition of different complexes of cyclin-cyclin dependent kinases (CDK). Incorrect expression of any of these cyclins leads to genetic instability. The CDK activity is determined by several mechanisms. Additionally, some cyclin-CDK complexes can be blocked. The binding of a growth factor to its receptor on the cell surface triggers the activation of certain pathways and further to the activation of some cyclin complexes which trigger the transcription and expression of the proliferative response genes that induce DNA replication and cell mitosis. Mature undifferentiated stem cells support tissue regeneration when they proliferate being exposed to certain stimuli. The knowledge of the mechanism determining when, where and why stem cells start to regenerate or differentiate is limited though their microenvoronment was shown to produce necessary signals shaping further behavior of these cells [17,18].

The accumulation of cellular metabolites has a detrimental effect on cell components and functions, induces changes in tissue homeostasis and ultimately produces a critical damage of the whole organism. There are different medical conditions associated with enhanced accumulation of

cellular metabolites such as lipids (lipidosis, steatosis), cholesterol and its esters, proteins, glycogen, pigments (chromoproteins, lipofuscin and melanin), bilirubin, calcium, hyaline and so on. Water-electrolyte imbalance with fluid retention is yet another important factor. The accumulation of cellular metabolites leads to cell enlargement and aggregation, and reduction of the intercellular space. Under these conditions, the cell cycle becomes unstable, autophagia is reduced, the production of the target of rapamycin (TOR) is increased while that of sestrins is reduced. All this impairs cell recovery and antioxidant mechanisms. The oxidative stress caused by lipid peroxidation, oxidation of proteins and oxidative modification of the genome, mitochondria and DNA plays an important role in oncogenesis. Autophagia helps cells get rid of damaged mitochondria and replace them with new ones. Aging mitochondria produce high levels of active oxygen species or free radicals that destroy tissues. Autophagia is reduced with aging, which enhances the accumulation of damaged proteins prone to aggregation.

Sestrins produced by stressed cells activate AMP-activated protein kinase (AMPK) and inhibit target of rapamycin (TOR). AMPK and TOR are two protein kinases that are very important regulators of metabolism and aging. When the release of metabolites from the cells is restricted, TOR production is increased while that of sestrins is reduced. AMPK is activated in response to a reduction in energy utilization (a factor slowing down the aging process) while TOR is activated in response to excessive energy level at which aging is faster. AMPK activation inhibits TOR, and drugs that activate AMPK and inhibit TOR can slow down the aging process. Accumulation of aging cells associated with a reduction in the number of stem cells diminishes the proliferative potential of regenerating tissues, stimulates cell division and initiates tumor growth. Tumor growth is constrained by normal healthy cells. The processes are slow while proliferative cells are still in contact with tissue matrix and normal cells. When cellular receptors of the cell division inhibitors are blocked but the cell is stimulated for division it acquires new characteristics and enters into a state of spontaneous division. This is manifest as a rapid tumor growth (expression).

TRANSGENIC TUMORS

Transgenic tumors are a result of incorporation of some viral or bacterial genetic material into the genetic apparatus of the cell. This gives rise to a foreign microorganism the behavior of which is determined by its own capabilities and its environment. The fate of this hybrid is determined by the immune and hormonal systems of the macro organism and the biopolicy of other microorganisms.

As was shown in the 50s of the last century, viruses can become incorporated into DNA cells and replicate with them. Modern genetics has established the existence of horizontal gene transfer, which allows assuming that a combination of the genetic material of microorganisms with the cells of the macro organism is quite possible. The cell genome receives new information that distorts its life cycle and changes its biology [19-22]. The data presented in the review are convincing but their interpretation can be different. As is generally accepted, viruses and microbes change the cell genetic apparatus and transform a normal cell into a tumor cell that will be similar to cells of other tumors. I believe that this hybridization results in the appearance of a separate entity, a new microorganism with new features and obeying its own laws. Colonies of such cells are actually tumors that differ from other tumors by their origin and structure. The behavior of the hybrid microorganism is determined by the immune system of the host, its interaction with other microorganisms, by the extracellular matrix, surrounding cells and division activators. They do not have division inhibitors. It should be noted that some carcinogens destroy the extracellular tissue structure and thus change the normal proliferation process, contributing to a faster penetration of the virus into the cell and formation of a hybrid.

Gestational tumors include tumors of dysembryogenesis, as well as germ cell tumors, trophoblastic and coelomic epithelium tumors.

The nature of induction influences as well as causes and mechanisms of cell migration are not yet fully understood. It is still unclear what changes the migration of sex cells. We still do not know the mechanisms underlying the division of the internal cellular mass (the embryoblast) and why they become faulty. I believe that faulty embryogenesis with migration of sex cells and division of the internal cellular mass is a cause of these tumors.

TUMORS OF GENETIC ABERRATIONS

Scientists know several hundreds of hereditary biochemical defects in the human body, caused by changes in the genetic constitution of the individual [23,24]. The hereditary aberrations of the *p53* gene are associated with the violation of DNA repair, which cause breast cancer, sarcomas, leukemias, CNS tumors, adrenal tumors, epithelial tumors. Some chromosomal rearrangements play a leading role in developing congenital and hereditary human oncological diseases.

DISCUSSION MATERIAL

Numerous publications in this area show that there is no clear understanding of what happens in oncological diseases. No hypothesis can explain spontaneous malignization *in vitro*. None of the existing hypotheses is universal and covers all mechanisms of carcinogenesis. Ideas generalizing available findings are yet to be postulated. The concept that all tumor types have the same cause has never been validated and the treatment of cancer is still a serious medical issue.

Oncological diseases are believed to be caused by carcinogenic factors [25-28]. The very word carcinogen means a source, inductor, trigger of tumor. They are but a component of some carcinogenic mechanism rather than the primary cause of cancer. Moreover, tumors can grow even in the absence carcinogenic factors. Carcinogenesis can be stimulated by certain hormones and vitamins that activate cell division accelerate metabolism and increase the production of cell metabolites which tend to accumulate in the tissues. While the negative role carcinogens play in dysembryogenic tumors is not yet established, in tumors of malignant proliferation they damage the architectonics of cells and extracellular matrix, impair the clearance of cellular metabolites, cause a reduction of the intercellular space and increase cell aggregation. In transgenic tumors, they facilitate the penetration of viruses into the cells.

My remarks on carcinogenesis should be regarded as a stimulus to the search of other explanations of carcinogenesis rather than criticism of the role carcinogens are believed to play in this process. The oncological concepts presented here are based on the extracellular theory [13], which holds that the life and behavior of the cell is completely determined by extracellular materials in its microenvironment. My concept is well in line with the tissue theory of cancer proposed by Cherezov [29], though I do not believe that there is a common denominator for all carcinogens and all cancers as their etiology is different.

Aging is but a part of the carcinogenic mechanism in the organism. The latter also includes autoimmune processes and exposure to surfactants. The mechanisms of aging, cell cycle and DNA repair are intensively studied in different countries as oncological diseases are associated with impaired mechanisms of cell proliferation. Aging is mainly related to the aging of collagen and extracellular matrix dysfunction causing aging of cells which lose their ability to self-regeneration and reproduction, to store hereditary information and restore it in case of failures [17,18]. The growth of tumors is determined by numerous factors at work not within individual cells or limited "tumor field" but in the whole tissue or body. Tumors can start growing either consecutively or synchronously in different tissues. Tumors appear at sites where the impact of negative factors is the strongest. Widely used domestic surfactants as a factor of carcinogenesis are underestimated. Even in minimal (trace) amounts, surfactants absorbed with food change intercellular interactions and adhesion.

Petrov [30] pointed out that tumor cells do not have a universal morphological feature that will distinguish them from normal cells. As we know, tumor cells are not characterized by some specific protein, enzyme or fermentation reaction that cannot be found in normal cells at some stage of ontogenesis. Human tumors are shown to contain no antigens that cannot be found during the normal embryonic development of tissues. There is no genetic defect such as loss or appearance of a new product encoded by some gene that will be common for all malignant tumors. Malignancy of cancer cells is not inherited as daughter cells can normalize. Thus fibronectin added to cultured cancer cells of malignant proliferation significantly improves adhesion [31-33]. The addition of fibronectin restores the normal highly ordered distribution of a major cytoskeleton component – the network of filaments made of protein actin. These facts plus a gradual growth of tumors from initial precancer lesions run counter the concept of mutational changes causing cancer and indicate that the course of events leading to cancer is different. Nevertheless, a cell of malignant proliferation cannot be called normal as its "young' features become manifest not in the right place and at the right time. Such an aberrant behavior can be a result of either deficit or excess of substances normal cells are composed of.

Compromised immunity is believed to be closely associated with cancer [34-36]. When the immune system functions normally it can rapidly eliminate appearing cancer cell. The role of the immune system in the control of transgenic tumors, like of other infections, is indeed critical but the immune system cannot cope with tumors of malignant proliferation and dysembryogenic tumors as it cannot differentiate their cells from normal ones, irrespective of its status. The immunity status determines the autoimmune response. Thus systemic autoimmune diseases of the connective tissue have an impact on different organs and are manifest as fibrinoid necrosis. Autoantibodies that are formed in this process interact with the DNA and other cellular components such as cytoplasm and cytoskeleton (and its actin), as well as with matrix collagen [37-39]. Structural changes in DNA lead to functional changes and then to the death of cells, which stimulates the division of other cells. Malignant proliferation is not possible if the cytoskeleton is intact. It can be stimulated when division inhibitors are blocked as a result of damage of collagen in the extracellular matrix. Collagen damage of the extracellular matrix leads to blockage of the division inhibitors, which also contributes to malignant proliferation.

Further studies of aging and metabolic processes between the cell and extracellular matrix can shed light on the regulation of normal cell division process. Development of vaccines against non-transgenic tumors will be a futile exercise while in the treatment of transgenic tumors the use of new antibiotics and vaccines can be very effective. Induced immunity makes a significant contribution to the treatment of tumors.

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