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Views and Suppositions about the pathogenesis of Cancer

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PREFACE

Mankind, in particular its most intellectual stratum – scientists, can deservedly be proud of own progress in fighting some so far incurable infectious diseases, which used to do great harm to humans: smallpox has been liquidated, almost eliminated are Black Death, poliomyelitis; a great progress has been achieved in fighting tuberculosis, etc. At the same time, irrespective of great intellectual efforts and costs, some diseases, including primarily cancer, AIDS and others, are still beyond the human control.

Among the leading factors of science advance are hypotheses and theories, which originate at different stages of development of individual scientific disciplines.

A modern researcher of carcinogenesis is faced with the principal dilemma: he/she must either acknowledge that cancer is caused by completely different in nature agents and factors or try to create a theory, which will incorporate this array of conflicting facts and which make it possible to establish not only the role of a specific agent or factor in the development of cancer but also (most important) the possible mechanism of their action.

In the cancer research there were periods, when the research proceeded under dominance of researchers of different specialities. This rather complex problem was studied first by pathologists, then geneticists, immunologists and virologists. Naturally, such dominance was not of absolute nature. Lately the entire burden of this problem has been assumed by biochemists and molecular biologists. These very specialists are to reveal molecular processes in the cell genome anomaly, which cause the tumor process. From them we should expect the development of such methods which would contribute to curbing the spread of the disease or even to the process of its cure.

Tumors are widely spread in nature, the cancerous growth being one of the main causes of human mortality. Almost all types of multicellular organisms are practically prone to develop various forms of malignant tumors. Cancer (osteosarcomas) has been found in buried animals, namely in dinosaurs, which are known to exist long before the origin of man.

A rather alarming trend of tumor growth and “rejuvenation” has been observed lately. The spontaneous development of tumors is also frequently noted in laboratory animals, which makes it possible to study the neoplastic process experimentally.

The discovery of physical and chemical carcinogens has initiated a rather important stage of the theoretical oncology development. Almost all the phases of cancer formation and development are now observable. In general, the development of theoretical oncology is the most enigmatic page of the biological science history.

Experiments to study the cancer development in animals using different tissue irritators (acids, alkalis, etc.) have been running long since. In 1915, K. Yamagiwa and K. Ichikawa successfully induced the first experimental cancer by repeatedly painting coal tar into the skin of rabbit ears. Thereafter, rather potent carcinogenic hydrocarbons were isolated: dibenzantracene, benzpyrene, methylcholanthrene, urethane, etc.

A great number of factors causing tumor transformation undoubtedly essentially reduce a possibility of finding the general cause of cancer and of developing the etiotropic therapy.

Frequently, carcinogens of different nature tend to interact in a synergic action rather than exclude each other. All carcinogens have the like principal signs and properties, which, in certain cases, essentially coincide.

The circumstance that the tumor transformation of a normal cell is not a direct result of the action of a carcinogen, e.g. after irradiation, is seemingly indicative that the true cancer cell originates following a definite sequence of events taking place only at the cell and organoid levels, which requires certain time.

What is a cancer cell? Or what is its essence? At the current stage of development science has no answers to these questions. And by now, unless we understand the genuine nature of cancer cell, its essence, it would nor be real to think about the development of effective methods of treatment of this fatal disease.

It has been established that cancer cells gradually lose the structural and functional differentiation. At this stage, they become independent from the systems regulating the organism and corresponding tissues. One of the demonstrative examples of such autonomy is the tumor growth in a starving man, when normal tissues experience atrophy. A complex of cancer cells, as compared with the initial tissue, is of a more primitive structure, is anaplastic. For example, anaplastic cells of the mucosa sometimes do not mucify at all; the muscular tissue tumor loses compressibility and thus the main function of a living cell – specific synthesis of a respective tissue is altered. Some tumors start synthesis that is characteristic of the embryonic period.

In the opinion of the absolute majority of researchers working on the problems of carcinogenesis, the genetic apparatus of the target cell should be responsible for the conservation of a tumor cell from the normal cell. The role of non-DNA cellular elements in carcinogenesis has received little attention. A role for the plasmalemma in carcinogenesis has been proposed previously [1-4]. Out of the works dedicated to this subject (or the role of plasmalemma in forming a cancer cell) the most important, in our opinion, were the data of B. Israel and W. Schaeffer of 1988 [5]. It has been shown that fusion of cytoplasts from tumor cells with karyoplasts of normal cells resulted in a 97% incidence of tumors, while the opposite combination - fusion of normal cytoplasts and tumor karyoplasts yielded 0%

tumors in rats. At the same time, some scientists have proposed that genetic changes in carcinogenesis are on secondary place after unknown events on sub-cellular level [6]. Some scientists postulate the primary defect in carcinogenesis to be structural changes in the plasmalemma that result in loss of electron homeostasis [7].

However, the mechanism by which structural and biophysical changes of plasmalemma become persistent and heritable and their precise role in malignant transformation are unclear.

The essential positions of the karyogamic theories and malignant neoplasms genesis may be formulated in the following way: 1) malignant neoplasms may arise spontaneously, and also after the action on normal cells of various agents and factors of different nature. Primary target for carcinogens are determinants of cellular membranes, but not cell's DNA; 2) on the first stage of carcinogenesis (initiation) two normal somatic cells of one organ or tissue may create dikaryons - hetero- or homokaryons, but in some cases nonviable polykaryocytes. Presumably, during the perforation of cellular membranes induced by different carcinogenic and non-carcinogenic factors, the total charge of plasma membranes changes and the cells acquire the capability of closely approaching (adhesion), which frequently, especially upon coincidence of the perforated parts, may serve as a prerequisite to fusion process; 3) as a result of karyogamy, i.e. after synchronous mitosis or simple mechanical assembly of nuclei of hetero- or homokaryons, mononuclear hybrid precancerous cells develops, with tetraploid set of chromosomes on initial stage of hybridization. This is precancerous (initiated, immortal) cell, which exists in organism indefinitely long time; 4) influence of physical, chemical, and biological carcinogens on cells, is probably adequate. On the promotion stage, after the influence of complete (full) carcinogens or promoters on tissue, where precancerous synkaryons pre-exist, the chromosomal aberrations of different types and genes amplifications may arise in these cells. After the above-marked conversion on sub-cellular and molecular levels there may arise true cancer synkaryon – the malignant cell with the ability of uncontrolled proliferation. This cell represents clone, from which formation of malignant tumors substrate on early stage of carcinogenesis begins; 5) in a timorous synkaryon, in particular in its plasma membrane, most probably the antigenic mosaic of normal precursor cells is inherited, and due to this fact, such cells "escape" from the immune forces of the macro organism. And, actually, no specific tumor antigens, ferments, or the characteristic only to it different proteins, lipids, glycolipids or other chemical substances have been found in a cancer cell, which are not characteristic of normal cells at various stages of their life path; 6) in the process of tumor progression (concretely, invasion) after the segregation of some chromosomes, there may arise tumor cells with aneuploid or even hyperdiploid set of chromosomes. In extremely rare cases, tumor cells possess even diploid, hypodiploid or even hyperhaploid sets of chromosomes; 7) In the process of tumor progression (more specifically, invasion) segregation of some chromosomes in the tumor synkaryon, and also involvement last cells by means of fusion of considerably amount of other tumor

cells and normal cells of different types and maturity take place. After this tumor cells with extreme polymorphism of karyotype and new abilities, arise. Evidently, the membrane potential of a cancer cell plasmalemma should be connected with the changes of physical and chemical nature occurring in the body, as well as with the metabolic activity of this type of cells proper. In the case of a relatively suppressed metabolism of cancer cells, the environmental pH increases. And in the case of high pH, a cancer cell may develop a high negative charge, which suppresses its adhesion with the tumor bulk and can lead to its detachment and migration in the macro organism (metastasis).

We have already published 4 books dedicated to the hybrid nature of cancer cell. One book is in Georgian (1993), the second - in Russian (1993), and in 2010 and 2013 monographs under our authorship were published in New York and Saarbrucken, dealing with the possible mechanism of malignant transformation of a normal cell [8,9]. They contain many facts in evidence of this idea, in terms of experimental and clinical medicine.

What did condition the idea of writing this monograph? And in what does it differ from its fore-runners?

This the final attempt of writing a monograph dedicated to this subject (since all such earlier attempts, in the form of articles or monographs, with rare exceptions, have turned to be a “voice crying in the wilderness”). The main emphasis in this monograph, in contrast to the earlier monographs, is made on the first stage of carcinogenesis - namely on the initiation, which is discussed in detail (as far as possible!). The main steps of this stage, particularly the plasma membrane perforations and the resultant dramatic for a macro organism conditions, develop at the stages of cellular and sub-cellular levels. Moreover, as it has been found and as we will further see in all the chapters of the monograph, absolutely all carcinogenic agents, factors or effects are capable of forming in plasma membranes of target cells, the so-called pores, which in some cases may precondition the dramatic processes going on the cellular and sub-cellular levels.

Along with the experimental and clinical data, the opinions of theoretical nature, suggestions, etc., are given in this monograph to substantiate the karyogaimc theory of carcinogenesis.

In addition to the data evidencing the hybrid origin of a cancer cell, this work attempts to answer some important and still unanswered questions of modern oncology: 1.What is a cancer cell? 2.What is the essence of the common mechanism of action on the somatic cells of diametrically different carcino-gens? In other words, how can so etiologically different factors, such as viruses, irradiation, chemical carcinogens, toxins, etc., cause the adequate carcinogenic changes in the target cell? 3.How the effects developed on the cell surface, in particular on the plasma membrane, cause hereditary changes in the cell genome? 4.Are the somatic aberrations the initial or secondary effects of carcinogenesis, etc.?

The book consists of 10 chapters with the seemingly radically different headings and contents, the unifying idea of which consists in the participation of diametrically different carcinogenic agents in the effects developed on the plasma membrane of somatic cells of different type, namely in perforations and follow-up somatic hybridization. Special attention is given to the evidence of the reality of initiation as the first stage of carcinogenesis, as well as the detailing of different steps of this stage.

The SUMMARY, given in the end of the book, is quintessence of the entire monograph being presented in the form of final conclusions.

The present monograph is not a manual to be read in succession, from the beginning to the end. Therefore, some main concepts, provisions are sometimes, although shortly but still, repeated in some chapters and sub-chapters. This will, to our mind, save the reader from unnecessary looking for a specific chapter or sub-chapter dealing with the specific subject.

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1 PRIMARY TARGET FOR CARCINOGENS

The study of a plasma membrane acquires a great importance in pathocytology, because it enables to obtain important data on the physiology and pathology of a cell. The critically important for a cell function – penetration, is closely associated with the plasma membrane. By means of this organoid a cell receives all necessary substances for extracting the final products of metabolism.

Any damage of a plasma membrane (e.g., perforation) by different effects leads to a direct contact of the damaged section of the cytoplasm with the environment, which might, in the case of large volume (size) of pores, cause the cell's disintegration.

The principal components of plasma membranes are lipids and proteins. Almost one-half of the mass of plasma membranes of mammalian cells is lipid. It is conventional to place the lipids in three different categories: phospholipids, neutral (uncharged) lipids (such as cholesterol, which is usually found in large amounts in plasma membranes, but not in intracellular membranes), and glycolipids. The lipids in membranes are arranged so as to accommodate their amphipathic character. They form a bilayer, who layers back to back, so that their hydrophilic heads constitute the top and bottom surfaces of the membrane and their hydrophobic tails are buried in the membrane interior.

Membrane proteins can be divided into two classes depending on their location with respect to the lipids of the membrane framework. 1. One class consists of those protein molecules that are associated only with the membrane surface. These proteins are located adjacent to either the outer or the inner surface of the membrane. 2. The second class is made up of proteins that actually penetrate the membrane surface. These proteins enter the lipid bilayer and sometimes extend all the way through it.

In the opinion of some scientists, especially of adherents of virus-genetic theory of carcinogenesis, it is hard to imagine that influence of cellular surface by different carcinogens may alter cells' genome; moreover, that inherited character of malignant transformation supposed exactly the cellular genome alteration. From the position of the karyogamic theory, the action of any carcinogen is not associated directly with gene apparatus of cells. Alteration of the cell's genome is induced indirectly; that is, after the somatic cells' fusion and arising of precancerous, tetraploid cell.

Thus, both viruses and other carcinogens of other nature contain in their primary target a plasmalemma of somatic cells rather than a genetic apparatus, as most suppose. Consequently, the primary and the principal target of different carcinogens (for example, viruses) is the plasma membrane of the cell. The irreversible damage of this organoid becomes the cause of the destruction of the cytoplasmic organoids and the cell as a whole. Some virus (and other carcinogens) through massive perforations of the plasmalemma, deranges homeostasis of the target cell, in particular, its metabolism, to which the cell respond with a whole series of second-order reactions. It is possible that upon massive attacks by the virus on the cell, formation of multiple disintegrations (perforations) in the plasma membrane, and penetration into the target cell, the same pathogen damages other membrane organoids of the cell as well (for example, lysosomes, mitochondria, endoplasmic reticulum, etc). To this should be ascribed the development of second-order morphological and functional changes in the target cell (for example, autolysis).

Presumably, any microtrauma of the cell surface provokes first of all injury, lysis definite part of plasma membranes. As it seems, upon massive infection of the plasma membrane and formation of pores of definite size, the cytoplasm gets in direct contact with the environment. And such type of a contact lead to the cytoplasm disintegration accompanied by edematization of its structures, enlargement of the sizes of the nuclei (disintegrative swelling), active movement of the ectoplasm as well as the cytoplasm, translocation of granules towards the nucleus zone. The cytoplasm consistently becomes diluted, indicative of which is the Brownian motion intensification. At the subsequent stages of cytopathology, when active destruction of the cellular organoid takes place, the damaged cell releases different intracellular components or their fragments: mitochondria, lysosomes, ribosomes, endoplasmic reticulum elements, intracellular vacuoles, lipid granules, disintegrated nucleus fragments, elements of the plasmalemma proper, essential for cell existence enzymes (e.g., protein kinases), etc., which catastrophically deranges its homeostasis. Thus, the carcinogenic and infectious processes, in spite of their principal difference (proliferation of target cells, in one case, and destruction - in the other), can be induced by the same agents (e.g., virus).

As regards the carcinogenic (initiated) action of some viruses, according to the karyogamic (hybridizationtheory, theory of “two synkaryons”) of carcinogenesis, the primary and principal target of the virus (and other carcinogenic agents) is not the genetic apparatus of the somatic cell but the determinants localized on the cell’s plasma membranes.