DDC-UDC 616-006.6-092
Anzeige – Info@dwherold.de
DOI:10.19221/2017114

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INVOLUTION THEORY OF CARCINOGENESIS AND POSSIBILITY OF ITS APPLICATION IN THE TREATMENT OF CANCER (Literature rewiew)

Abstract. *The essence of involution theory of carcinogenesis is that deterioration of conditions of the human body cells existence caused genetic transformation of one of these cells into a primitive form of a single-cell elementary organism helping their individual survival. Application of physical and chemical (pharmacological) factors of influence directed to deterioration of existing conditions of transformed malignant cells and improvement of conditions for the existence of cells in the macroorganism should improve the results of patients suffering from cancer.*
Key words: *cancer, carcinogenesis, treatment.*

The word "carcinogenesis" originating from two words – Latin "cancer" and Greek "genesis" meaning development or origin – is a complicated process of origin and development of cancer. Tumour process refers to the group of polyetiological diseases, thus there is no a single main factor available promoting the development of tumours. The disease occurs in case of combination of numerous conditions and factors, and inherited susceptibility and natural resistance are of certain importance as well. Cancer is incurable at late stages of the disease.

There were numerous suggestions stated concerning the causes of cancer. Although, there are comparatively few real scientific hypotheses formed on a strict analysis of undisputable factors.

In the work written by the English physician Percivall Pott "On Chimney Sweeps' Scrotum Carcinoma" published in 1775 cancer was considered as an occupational disease. Chimney sweeps were exposed to soot penetrating through the skin, and in 10-15 years they got skin cancer. Two main factors were found causing development of cancer: 1) continuous irritation and damage; 2) exposure to certain substances named carcinogens. Explanation of the mechanisms of this form of cancer initiated a new era in investigation of tumour process. In 1853 the German scientist Rudolf Virchow suggested his "theory of irritation" explaining the causes of carcinogenesis in case of repeated mechanical or chemical damages of tissues. Ling cancer of smokers is caused by a number of factors: high temperature generated during smoking, chronic bronchitis provoking active proliferation of the epithelium, carcinogens available in tobacco. Nowadays smoking, alcoholism, chemicals (carcinogens), exposure to toxic industrial wastes, chronic diseases, viruses, protozoa, fungi, deterioration of ecological situation, radiation, inherited factors are considered to promote the development of malignant tumours. More than 1000 carcinogenic substances of an exogenous (external) and endogenous (internal) nature are described now. However, soon after Virchow's theory certain difficulties appeared: irritation and carcinogenic effects did not always correlate with each other. Moreover, simple irritation did not always result in cancer development. For example, 3,4-benzpyrene and 1,2-benzpyrene possess practically similar irritating action, although only the first compound is carcinogenic.

The end of the XIX century was marked by flourishing of microbiology and origin of virology. Many laboratories of the world were looking for "a cancer agent", and in 1911 the American physician Peyton Rous managed to prove a viral nature of certain tumours in chickens. He obtained an extract from chicken sarcoma that did not contain any cells. Injection of the extract to healthy chickens resulted in the development of tumour in the place of injecting (P. Rous was awarded with the Noble Prize for his experiments in 1966). The virus incorporates into the cellular genome bringing additional information to the cell causing disorders of the genome and cell vital activity. Viruses are able to persist in cells for a long time being in latent condition, and under

effect of carcinogens and physical factors they are activated. Although, by means of viral theory we are not able to explain why cancer does not possess signs of an infectious disease, and why tumours of different morphological types are found in relatives. For example, a wife was diagnosed with cancer of the lip, and her husband – with cancer of the stomach.

In 1946 Soviet microbiologist L.A. Zilber formulated viral-genetic theory of carcinogenesis disproving a number of difficulties of the viral theory (the phenomenon of non-transmitting cancer in particular). This theory later supplied by other ideas became a basis of modern conception of carcinogenesis. The theory of oncogene expression is in the basis of this theory. Oncogenes are genes promoting development of tumour process. Oncogenes were discovered in viruses – viral oncogenes, and similar o them were discovered in cells – cellular oncogenes. Oncogenes are structural genes coding proteins. They are inactive and repressed, therefore they are named proto-oncogenes. Under certain conditions oncogenes are activated or expressed, oncoproteins transforming normal cells into malignant ones are synthesized. Conversion of proto-oncogene into oncogene is one of the mechanisms of occurring malignant tumours. Although, blanching phenomenon of tumour virus from cancer cells has not been explained yet.

In the 30-s of the XX century the German biochemists Otto Warburg indicated that fermentation intensity is 10-30 times as much in cancer cells. O. Warburg proved that tumour cells obtain essential energy for them as a result of glycolysis, and they absorb less oxygen than normal tissues. Therefore, O. Warburg suggested that the process of conversion of a cell into a cancer one is caused by mitochondrial damage – the respiratory apparatus of cells. According to O. Warburg's theory, transmission to oxygen-free method of energetics results in autonomous uncontrolled existence of a cell: it behaves as a separate organism seeking to reproduction. O. Warburg's ideas were proved in 1953 when other researchers enabled to convert normal cells into cancer ones by means of periodical continuous interruption of oxygen supply. Later there was found that together with intensive fermentation respiration occurs in cancer cells, thus these cells use energy from two usually mutually exclusive sources. It undermined the foundations of Warburg's cancer theory.

Julius Friedrich Cohnheim suggested the theory of embryonic germs of tumour growth. According to this theory a great number of cells are laid in the early embryonic period. Under unfavourable conditions (injury, immune suppression, and long mechanical irritation) they can initiate tumour growth. In different times this theory either provoked interest or experienced oblivion periods. Discovery of oncomarker alpha-fetoprotein, a protein characteristic for embryonic and tumour cells, promoted better understanding of carcinogenesis as a special form of embryogenesis. Cohnheim's theory explains the development of dysontogenetic tumour (teratoma, dermoid tumours). Although induction of experimental tumour by means of implantation of embryonic tissue did not bring convincing results.

The German scientist Hanselmann presented the characteristics of a tumour cell which was of a great importance for the development of study concerning the causes of tumour growth. He considered that it was a body cell that differed from the maternal cell by its special properties. These special peculiarities are morphologically manifested in reduced differentiation, and physiologically – in greater independence of these cells. Hanselmann defined different degree of differentiation together with ability to independent existence by the term "anaplasia". This term preserves its meaning till nowadays.

Parasitic theory came into being at the beginning of the XIX century. Karl Michael is regarded a founder of parasitic theory who considered tumour as an animal outgrowth in the form of a sponge growing into the afflicted organ. L. Pfeifer suggested that cancer is a parasitic disease caused by ameba. The Soviet Professor M.M. Neviadomsky in 1930-1950 considered that a tumour cell is a cell from protozoa which according to its cycle of development is close to Chlamydia class, and tumour is a colony of microparasites. Parasitic theory does not explain why a cancer cell usually preserves partial structure and function of that tissue (synthesis of specific proteins in particular) it originates from, even after metastasis.

Tumour transformation of cells is named malignization (malignant transformation). General signs of malignization are:

1. The cell is able to uncontrolled

demonstrative reproduction or division.

2. Disorders of cell differentiation are found, the cell remains immature and young.

3. Autonomic character, independence from controlling and regulating effects of the body. The quicker tumour grows, as a rule, the less differentiated cells are.

4. Ability to metastasis. Metastases are cells able to be transported along the whole body by hematogenous, lymphogenous or another way and form the foci of tumour process.

5. Malignant cell is characterized by morphological and biochemical atypical features [4]. In tumour cells the square of contact surface decreases, as well as amount of nexuses – contacts ensuring adhesive abilities of cellular membranes, the contents of membranous glycoproteins changes – carbohydrate chains become shorter. Embryonic proteins, not peculiar for mature cells, begin to synthesize in the cell, the number of phosphotyrosines increases. It results in disorders of the properties of contact inhibition, lability of membranes increases. Within the norm cells get in touch with one another, and they stop their division. In tumour cells the absence of contact inhibition results in uncontrollable proliferation.

Atypical character of energy exchange is manifested in prevailing glycolysis – an ancient kind of metabolism. In tumour cells negative Paster's effect is found, that is, intensive anaerobic glycolysis did not decrease during changing of anaerobic conditions into aerobic ones, it is preserved (intensified glycolysis in tumour cells causes their high survival under conditions of hypoxia). Tumour absorbs nutrients actively. The phenomenon of substrate traps is observed. It is an increased compatibility of the enzyme to substrate (glucose). The activity of hexokinases in tumour cells becomes 1000 times as much. Tumour cells are also traps for protein resulting in cachexia. Prevailing glycolysis causes increased concentration of lactic acid in tumour cells. Acidosis is peculiar resulting in disorders of vital activity of the cell itself (necrotic zone is usually located in the center of the cell). Therefore, tumour causes a negative effect on the whole organism. Intoxication occurs caused by the products of metabolism and tumour breakup. In addition, tumour deprives the body of essential nutrients, energetic substrates, and plastic components.

Suggested involution theory of carcinogenesis is a kind of synthesis to some extent and continuation of Warburg's theory, genetic and parasitic theories. Its sense is that the cause of malignant transformation of the cell is in its genetic transformation into more primitive form of a single-cell simplest organism characterized by autonomous and parasitic vital activity. This single-cell organism as compared to many-celled ones is on the lower stage of evolutionary development and belongs to the Animal kingdom – Animalia, subkingdom – Protozoa (the process of a reverse development in biology is termed involution). Although every transformed cell due to involution possesses certain advantages as compared to every separate cell of many-celled organism resulting in gradual expansion of these transformed cells along the whole body.

Involution conversions in the human body occur with age on all the levels – molecular, cellular, organ and on the level of the whole organism. Examples of molecular involution changes are so-called body-measuring meters – small succession of nucleotides at the end of chromosomes which become shorter with every division. Therefore cells of the many-celled organism can divide only limited times, approximately 50, and short body-meters are found in malignant tumours [7]. On the level of an organ the amount of stromal elements increases with age, usually the organ becomes less in its size and its functions deteriorate. Against the ground of organism changes growth, vision, muscular tonus, speed of reaction etc. are found.

Involution on the cellular level, especially under unfavourable conditions, for example, hypoxia, deteriorated blood supply, can be accompanied by acquired signs of protozoa single-cell organisms, in the first turn, anaerobic type of respiration. In certain cases ability to unlimited division appears – in this case cancer develops.

Hypoxia is considered today as a key factor of pathogenesis of malignant formations. There are experimental and clinical evidences that hypoxia of mast cells, that is, a low level of oxygenation, effects their growth, intensifies malignant progress and metastatic potential in particular, as well as reduces sensitivity to chemotherapeutical drugs and ionizing radiation [6].

Unfavourable conditions for the body cells in the form of reduced intensity of metabolism, changes of the body ionic balance, reduced

calcium level in particular, shift of pH medium into the acid side and some others are intensified in elderly people. These factors and involution changes on other levels of the human body promote involution on the cellular level. Therefore, involution theory of carcinogenesis answers the issue why cancer sickness rate increases with age.

Of course, there are some cases of different kinds of cancer in the young age (for example, Ewing's sarcoma, lymphogranulomatosis). Although it is rather an exception from rules, it does not exclude a general tendency to increased sickness rate of cancer with age. Oncological morbidity among children can be explained by the fact that cases of involution in the early age occur on other levels of the body (for example, involution of the thymus begins from adolescence). In addition, anemia occurs more frequently among children than among adults, and it causes hypoxia of tissues.

There is no doubt that the mechanism of malignant transformation is genetic, and changes touch upon hereditary cellular apparatus considering the fact that the following generations of cancer cells preserve all the main properties of the previous generation. It can be suggested that genetic mechanism of transformation of cells into more primitive existence is preserved in a multicellular organism for possible survival of every separate cell when unfavourable conditions occur. Hypoxia is one of the main unfavourable factors, and the cell temporarily passes onto anaerobic type of nutrition. For this passing to more or less autonomous existence under unfavourable conditions so-called proto-oncogenes are kept in the cell genome. After improvement of the environmental conditions a reverse transformation of cells and their return to normal condition can occur. It occurs with the majority of such transformations that do not cause diseases. Although, in case a reverse development of cells after improvement of external conditions of their existence did not happen, it can be a cause of formation of benign and malignant tumours. According to this theory proto-oncogenes should be contained in the genome of protozoa and embryonic cells as normal genes coding proteins ensuring the ability of cells to anaerobic respiration, accelerated division, and autonomous vital activity.

E general amount of genes in the human genome is approximately 100 000. There are about 100 real proto-oncogenes among them, that is, cellular genes. Disorders of their normal function can result in their transformation into oncogenes and tumour transformation of cells. Transformation of proto-oncogene into oncogene leads to the synthesis of oncoprotein. Under the effect of oncoproteins the regulation of cellular growth, proliferation and differentiation are disturbed, appropriate conditions are created for accelerated replication of DNA and continuous distribution of cells.

Therefore, genetic transformation of certain cells of the body into the single-cell protozoa helps individual survival of cells, but it results in gradual death of the macroorganism. Such survival mechanism of multicellular organisms under conditions of hypoxia and deterioration of environmental conditions seems to be a universal one in the animal plant worlds, and it is genetically formed. In the majority of cases it helps to overcome a prolonged deterioration of existing conditions, and after improvement of these conditions the normal cellular structure is restored. Although the border, when uncontrolled division of a transformed cell occurs and the immune system is not able to manage it, is very fragile. In exceptional cases when this border is overcome the individual dies. Although, the existence of such mechanism provides certain advantages for the survival of the majority of organisms belonging to a certain biological species. In a small amount of organisms this mechanism breaks which is not marked on the survival of this species of organisms in the whole.

After involution malignant transformation the cell ususally is able to perform its functions peculiar before transformation, but not completely. For example, melanoma cells produce the pigment melanin, the cells of osteogenous sarcoma – osseous tissue, the cells of thyroid cancer – thyroid hormones etc. This functions of the malignant cells is usually pathologically changed (the osseous tissue is produced by the cells of osteogenous sarcoma in disorder), but its availability often helps to diagnose (detection of hyperproduction of specific hormones) and treatment (selective method of radiation therapy by radioactive iodine of thyroid gland cancer).

Proto-oncogenes can be activated by oncogenic viruses, although this mechanism cannot be

considered as the main one, because in practical medicine we do not observe cases of viral infection of people from others by the viruses of the most spread kinds of cancer by the type of viral hepatitis, flu etc. In addition, cancer more often occurs among people of an elderly age that cannot be explained by viral pathology. In general, many similar signs can be found in the structure and functioning of malignant cells and protozoa. Such peculiar similar signs can be presented in the Table 1.

Although cancer is not parasitic disease these signs cannot be neglected. In particular, Ukrainian researcher D.G. Zatula found similarity of antigenic structure of malignant cells and microorganisms [1]. In addition, examples from radiation diagnostics and radiation therapy of

Table 1

№	Malignant cells	Protozoa
1.	Malignant cells are able to reproduce themselves continuously, avoid protective mechanisms of the body and regulation by the body	Parasites intensively multiply to preserve their population. After they penetrate into host organism they avoid protective mechanisms of the body and do not submit to the regulation by the organism
2.	Autonomous, unlimited growth of the amount of tumour cells resulting in tumour formation	Colonial method of existence is a feature of certain protozoa. For example, volvox forms a colony as a result of uncompleted multiplication. The colony is more vigorous than single cells.
3.	Reduced requirement of neoplastic cells in external proliferation signals – so-called anchorage-independence, at the same time the majority of normal cells are able to multiply only under conditions of their fixation to a certain non-cellular matrix	Protozoa are able to multiply without substrate in liquid nutrient media
4.	Proliferation of the majority of tumour cells in the form of asymmetric amiotic division, while normal cells multiply by means of mitosis	Protozoa are multiplied by means of sexual and non-sexual ways. The most spread non-sexual way is division in halves (amitosis)
5.	Tumour cells differ from the normal ones by their size, ratio of the volume of the nucleus and cytoplasm, peripheral location of the nucleus, availability of one or more nuclei, absence of the nucleus and nucleolus, different set of chromosomes even within the limits of one tumour	Polymorphism of protozoa is explained by their nonsexual multiplication. Different amount of chromatin is the result of proliferation and isolation from the maternal cell several daughter cells with various amount of chromatin. The nucleus can be of a different shape, dislocated peripherally often
6.	Ability of tumour cells to metastasis includes ability to isolate from the general mass of tumours, move and secrete proteolytic enzymes	Isolation from the content of colonies of separate cells and initiation of new colonies - it is the property of colonial protozoa
7.	Tumour cells secrete metabolic substances having a negative effect on the body. Patients with cancer are characterized by anemia, cachexia, general metabolic disorders, low immunity, disorders from the side of the nervous system	Parasitic protozoa secrete metabolic toxins and enzymes (lactic acid, hydrogen peroxide, hyaluronidase, catalase etc.) due to which anemia, cachexia, disorders in the work of the organs and systems of the body
8.	Intensified anaerobic glycolysis by tumour cells even with presence of oxygen is their main difference from normal cells	Anaerobic glycolysis originates from that ancient epoch when in the atmosphere of the Earth oxygen was absent, and single-cell organisms existed due to glycolysis. Contemporary protozoa have kept the property of their ancestors till now

oncological patients can be given. Metastasis into the human brain on the images obtained by means of computed tomography and magnetic resonance imaging are similar to those injuries of the brain caused by toxoplasmosis. Treatment with metronidazole – electronic acceptor junction imitating oxygen action (its likelihood to electron) – is a known method to intensify efficacy of radiation therapy of malignant tumors [3]. At the same time metronidazole is the main drug to treat trichomoniasis caused by single-cell microorganisms.

On the assumption of the suggested involution theory of carcinogenesis increased probability of tumour metastasis after its biopsy, non-radical surgery, non-radical chemo- or radiation therapy can be explained by the attempts of autonomous tumour cells possessing the features of protozoa to find a safe place for themselves in the human organism – in bones, lungs, liver, brain. And the fact that after the course of radiation therapy radiologists notice the phenomenon of radioresistance [5] and increased proliferative activity of cells, can be explained by occurrence of new generations of cells after radiation acquiring stronger resistance to ionizing radiation and intensified their proliferative activity.

Existing today the main methods of treatment of malignant tumours are not sufficiently effective, as they are directed only to destruction of tumour elements and do not consider the conditions under which the tumour and organism exist during treatment. Chemotherapeutic, radiological, and surgical methods of treatment of cancer deteriorate general condition of a patient – anemia, leukopenia, intoxication with chemical preparations and radioactive substances occur (chemoradiation treatment), the patient is traumatized (surgical treatment).

Considering the above stated new trends in the improvement of treatment of oncological diseases so-called adjuvant therapy should be searched for in the means of physical and chemical effect improving the patient's condition and deteriorating conditions of tumour existence. In radiation therapy the means intensifying sensitivity of malignant cells to ionizing radiation are called radio-modifying. Besides a number of methods intensifying radiosensitivity of tumours are based on the use of oxygen effect [3]. Due to the fact that hypoxia is considered as a key factor of involution development of malignant cells, oxygenation of tumour and the organism in the whole should be improved by means of different methods. Restoration of the normal condition of the peripheral blood and prevention of anemia (as one of the factors preventing oxygen supply to the tissues) are one more compulsory element of the therapy of oncological patients.

The main principles of this theory were presented in the Ukrainian medical journal in 2008 [2]. There were no substantial critical remarks stated since that time. Publication in English will enable to make the range of scientists who will learn this theory wider.

Conclusions. 1. The suggested involution theory of carcinogenesis explains the problem of origin of cancer, its development and clinical signs best of all. 2. The essence of the theory is that under the effect of different pathogens (mainly hypoxia) genetic transformation of the cell occurs from activation of those areas of the genome that convert it into single-cell protozoa.

In the treatment of cancer those means should be used that improve oxygenation and blood supply of the tissues of patients, and eliminate anemia.

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