CANCER GENESIS: POSSIBLE MECHANISMS OF ITS DEVELOPMENT AND INHIBITION

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Abstract. *In this article the changes that may occur during transformation of malignant are analyzed and developed its further theories and novelties around the discussed topic.*
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During malignant transformation of a cell, a number of changes occur, starting with modification of the genetic apparatus and ending with the reversion of all balanced biochemical processes of its life. The accumulation of genetic and epigenetic damage in normal and then in aplastic cells leads to irreversible changes in metabolism and activation of systems aimed at increasing the survival of the transformed cell and its protection from fatal endogenous and exogenous influences. The beginning process of tumor progression indicates that the transformed cell has successfully passed the stages of initiation and promotion and has escaped the control of the antitumor immune surveillance system. A further consequence of the development of neoplasm is the production by the tumor itself of specific factors that suppress the immune response from tumor antigens and deprive the immune system of the ability to fight the pathological condition of the body. In addition, the development of a malignant tumor leads to a significant shift in the level of oxidative processes in the patient's body and an imbalance in the antioxidant defense system.
Numerous studies have shown that the increased formation of free radicals, which affect the activation of oncogenes and genome instability, is a factor in both the initiation and promotion of malignant cell transformation, as well as the processes of invasion and metastasis. Moreover, excess free radicals lead to tension in the redox balance in the cell, intensification of lipid peroxidation (LPO) of cell membranes, as a result of which membrane-bound enzyme systems are inactivated and intercellular contacts are disrupted. The dependence of the level of disturbances in the body's antioxidant defense system on the stage of the malignant process has been revealed.

It is believed that malignant transformation of cells is caused by the action of specific genes. The oncogenic theory of cancer has acquired a modern form in recent decades. According to this theory:

- oncogenes are commonly called genes that are activated in tumors, causing increased proliferation and suppression of cell death;

- non-mutated oncogenes act at the cellular stages of the processes of proliferation, differentiation and apoptosis, being under the control of the body's signaling systems;

- genetic damage (mutations) in oncogenes lead to the release of the cell from external regulatory influences, which underlies its uncontrolled division.

Another side of the problem concerning the mechanisms of restraining malignant transformation is associated with the function of suppressor genes, which normally have an inactivating effect on proliferation and favor the induction of apoptosis. Almost every tumor contains mutations in antioncogenes, as well as genetic instability.

In undamaged organs and tissues, cell death - apoptosis - is under strict genetic control. This is because apoptosis is a necessary process of cell replacement and natural cell elimination.

At the genetic level, changes accompanying apoptosis are manifested by gene expression and translation of corresponding proteins. Activation of apoptosis executors is the result of a branched chain of biochemical reactions, the meaning of which is ultimately that almost any external damaging signal can lead to DNA fragmentation and cell death. In addition to DNA fragmentation, a reliable sign of apoptosis is the activation or induction of caspases. The use of immunohistochemical method makes it possible to detect these proteinases in the early stages of apoptosis.

The existence of specific chromosome changes that create conditions favorable to the appearance of oncological pathologies has been established. Recently, research in this area has attracted increasing interest.

It has been established that chromosomal breaks and rearrangements, mitotic non-divergence and other aberrations underlie the initiating stage of carcinogenesis. Signal individual genetic manifestations of cell variability are chromosomal changes, the frequency of which in the tumor simultaneously reflects changes in many structural and functional features of genes.

Thus, chromosomal aberrations are markers of gene changes, and cancer is the result of changes in regulatory genes.

From the standpoint of the genetic instability of tumor cells, qualitatively new stages of tumor development are also assessed, in particular the activation or inactivation of apoptosis and proliferation, which results in the biological progression of the tumor and its acquisition of new clinical properties, such as aggressiveness and high malignancy. Malignancy depends on the balance of genes that enhance or suppress it, located on different chromosomes. Therefore, the loss of certain chromosomes leads to an imbalance between cooperator genes, such as p53, bcl-2, PCNA. During carcinogenesis, the dose of these genes, that is, their expression, plays a huge role. Oncological practice in recent decades has been enriched with fundamentally new antitumor drugs, thanks to new technologies, the possibilities of radiation, combined and complex treatment of cancer patients have been expanded. However, aggressive specific antitumor therapy often aggravates violations of the main components of immunity, general resources of homeostasis, reduces the body's resistance, leads to secondary immunodeficiency, etc. Thus, disturbances in the state of the lymphocyte component of immunity were noted in 74% of cancer patients, and disturbances in the state of the oxidative-antioxidative system - in 80%. Further development of more effective means of treatment of oncological diseases is needed, aimed at changing the immunobiological and metabolic interactions of the tumor and the body.

It is known that recognition of tumor cells depends on the increased expression of antigenic determinants on its surface. Tumor location and extracellular availability of mucin MUC-1 makes this marker a suitable target for tumor diagnosis and therapy. 6 human fragments of ScFv antibodies were isolated and characterized, which can be used in the creation of anticancer agents. To assess the clinical significance of the immune response to MUC-1, circulating immune complexes containing encoded polymorphic epithelial mucin (PEM) were studied. Preliminary results have shown that the humoral response to PEM protects against disease progression, so the authors propose the use of synthetic peptides or glycopeptides containing an immunogenic mucin backbone as an anticancer vaccine. Radioimmunotherapy is a promising approach for the treatment of metastatic breast cancer (BC). Initial clinical trials using radioimmunoconjugates and more recent studies have shown antitumor effects in previously difficult-to-treat patients with minimal toxicity. Antibodies target specific epitopes of the epithelial glycoprotein mucin MUC-1

on the surface of breast cancer cells. In these studies, myelosuppression had dose-dependent toxicity. However, this toxicity has been successfully overcome through the use of autologous peripheral blood stem cell translation.

Epidemiological studies have shown the beneficial effects of anti-inflammatory drugs in cancer prevention. The mechanism of action of these drugs is due to the inhibition of cyclooxygenase enzymes (COXs). One of these enzymes, COX-2, is most expressed in breast cancer cells, in which it induces proliferation, angiogenesis, and inhibits apoptosis. Anti-inflammatory drugs restore apoptosis, reduce tumor mitogenesis and angiogenesis.

Tamoxifen has been used for systemic treatment of breast cancer patients for almost 40 years. The success of treatment primarily depends on the presence of estrogen receptors in breast tumor cells. The action of tamoxifen is to inhibit estrogen receptors and induce apoptosis, as well as arrest the cell cycle at the G1 stage.

Tamoxifen has been found to significantly reduce the risk of breast cancer in women with atypical hyperplasia or carcinoma in situ. E. Farczadi et al. studied the short-term (7 days) effect of tamoxifen on apoptosis, mitotic index, expression of p53, bcl-2, HER-2/neu in invasive breast cancer. After treatment, the expression of HER-2 and p53 decreased, but bcl-2 remained unchanged. Mitotic activity decreased slightly, apoptotic activity, in contrast to samples taken before treatment, increased in 6 out of 10 cases.

Although the primary mechanism of action of tamoxifen is considered to be inhibition of estrogen receptors, S. Mandlekar et al. showed the existence of additional mechanisms not related to estrogen receptors. Recently, raloxifene has been proposed for hormone therapy for breast cancer, which acts as an estrogen antagonist, interacts with lipid transduction cascades, covalently binds to protein and DNA, regulates growth factors, the expression of HER-2 and p53, induction of apoptosis and many other effects in the genome. It does not prevent ovulation in women with normal menstrual cycles.

The study showed that steroid hormones may be directly involved in the regulation of apoptosis in vitro, but whether this is due to blocking or activating the mechanism of these hormones is not known. Thus, the experiment observed a protective effect of progesterone against the apoptotic process during involution of mouse mammary glands in vivo.

An in vitro study using the T47D breast cancer cell line showed an increase in p53 gene expression and induction of apoptosis upon administration of progesterone.

It was found that 2-methoxyestradiol inhibits proliferation and angiogenesis, but induces apoptosis, independent of estrogen receptors A and B.

High doses of estrogen can cause tumor regression in postmenopausal women with hormone-dependent breast cancer. Other authors investigated the molecular basis of this process using LTED cells, derivatives of the MCL -–7 breast cancer line, obtained under conditions of long-term estrogen administration.

High concentrations of estradiol (0.1 mM) led to a 60% decrease in LTED cell growth and a 7-fold increase in apoptosis compared to control. Therefore, tumor regression induced by high doses of estrogen in postmenopausal women may be the result of estrogen activation of Fas-mediated apoptosis.

In a study by Rahman K.M et al. discusses the clinical indications, risks, benefits and mechanisms of action of estrogen receptor modulators and related structures, in particular indole-3-carbonal, which may open new avenues in the prevention or treatment of breast cancer.

Thus, anti-estrogen therapy with E2 antagonists is of great importance for patients with breast cancer. In this regard, there is significant interest in the development of combinations that can provide therapeutic value in hormone-dependent breast cancer without adverse risks and effects.

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Thus, some authors believe that malignant transformation is caused by the action of specific genes, others associate it with a dysfunction of suppressor genes, which normally have an inactivating effect on proliferation and favor the induction of apoptosis. The antitumor therapy used causes disturbances in the lymphocytic immune system in 74% of patients, and in the oxidative-antioxidative system in 80% of patients. The data presented indicate the need for further development of more effective means of early detection and treatment of cancer.

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