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Key models and theories of carcinogenesis

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A brief overview of the most well-known seven types of carcinogenesis models is presented. They include mutation models, genomic instability models, non-genotoxic models, Darwinian models, tissue organization models, inflammation models, and an integrated model. Each model has specific oncogenic factors that cause certain types of cancer, have their own mechanisms, and are based on certain mathematical models.

Keywords: carcinogenesis, models and hypothesis, oncogenic factors, molecular mechanisms, genetic and epigenetic alterations, mutations, tumor microenvironment

Introduction

Human malignancy is one of the most actual problems of modern humanity. Hundreds of years of research have not made it possible to treat yet, diagnose and save the lives of patients suffering from this type of disease 100 % effectively.

Carcinogenesis is a multistage process that has the following stages of development: tumor initiation, promotion, progression, and metastasis [1]. It is still not known for certain which changes are highly specific to each stage, but it has been found that both genetic and epigenetic changes and abnormalities in the expression of many genes occur during all stages of the disease [2, 3]. However, it is precisely this diversity of molecular aberrations that poses problems in the diagnosis, treatment, and prognosis of the disease.

Today, there are a number of models and theories of the origin and development of malignant tumors that take into account already known genetic and epigenetic disorders in cancer cells, changes in the metabolism of cancer cells and the tumor microenvironment, and the emergence of systemic alterations in the human body.

Models of carcinogenesis

There are 7 types of the most common and well-known models of carcinogenesis (Table 1).

Table 1. **The main properties of the most common types of carcinogenesis models**

№	Model/ Characteristics	Oncogenic factors	Examples of factors/ specific cancers	Mechanisms	Mathema-tical model
1	Mutational models	Carcinogenic agents	Chemical, physical, biological (viral, bacterial and other) carcinogens	Genomic DNA alterations, mutations, activation of oncogenes	Armitage-Doll
2	Genomic instability models	Hereditary factors, genomic instability	Retinoblastoma and familial colorectal cancer	Chromosomal and microsatellite instability, repair of unpaired bases, inactivation of suppressor genes	Knudson
3	Non-genotoxic model	Clonal expansion/ epigenetic alterations	Diet, hormones, chemical influences	Methylation and acetylation of histones	Moolgavkar
4	Darwinian models	Clonal expansion/ cell selection	Mutagens, selectogens, chemotherapy	Acquisition of selective advantages	Nowak
5	Tissue organization model	Microenvironment, violation of the steady state of differentiated tissues	Focal proliferative alterations	Metaplasia at the junction of two different morphostatic fields, morphostats	Baker
6	Inflammation model	Oxidative stress, hypoxia, disruption of the microbiome, pathological aging	Immune dysfunctions, oncogenic viruses and bacteria, lifestyle features	Multiple inflammatory and oxidative hits, chronic inflammation, transformation of microenviron-ment into a tumor-supporting one	Okada
7	Integrative model	Reduced redundancy of healthy functional tissue units	Emergence Framework	The emergence of a new ‘system’ that has lost its normal self-organization arrangement and function. The dynamics of which can be studied via a state-space approach	Sigston and Williams

The first type of model is Mutational one. It was founded by the German biologist Theodor Boveri in 1914. This theory was developed by Hermann Müller, Alfred Knudson, Robert Weinberg, Bert Vogelstein, Eric Fearon, and others for almost a century [4]. The main idea is that genomic DNA mutations in cells are the main feature of carcinogenesis, leading to the appearance of a malignant phenotype [5, 6]. An early mathematical model by Armitage P. describes an increase in the frequency of mutations with age, which leads to the disorders necessary for the onset of cancer. Chemical, physical, and biological carcinogens were later identified as the factors causing the appearance and accumulation of muta-

tions [7–9]. Among biological carcinogens, oncoviruses play a significant role. The most dangerous and widely investigated oncoviruses include: hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomavirus (oncogenic variants) (HPV), Kaposi's sarcoma herpesvirus, human T-virus (HTLV-1), Merkel cell polyoma virus (MCV); Epstein-Barr virus (EBV), cellular lymphotropic virus, and others [10, 11]. In addition, relatively new candidates for oncoviruses are adeno-associated virus-2 (AAV-2), human herpes virus-6 (HHV-6), and human cytomegalovirus (CMV) [12–14]. Each type of carcinogens has its own mechanisms and peculiarities of influence on carcinogenesis and requires a separate analysis.

The second model is "Models of genomic instability". It characterizes two areas of research related to hereditary cancers: retinoblastoma and familial colon cancer. The first model was proposed by Knudson [15, 16] for retinoblastoma as a two-strike theory.

At that time, a new type of genes critical for the appearance and development of tumors was discovered — tumor suppressor genes. Inactivation of the suppressor gene *RB1* is a necessary factor for the development of retinoblastoma. According to Knudson's theory, in a hereditary type of cancer, the inactivation of one allele of the *RB1* gene is congenital (germline) and the second allele of the RB1 gene is somatic (mutation/inactivation), while in nonhereditary cancers, both mutations/inactivations of *RB1* alleles are somatic [15, 17].

The second area of research on this model concerns familial colon cancer, which is associated not only with the disruption of the *APC* suppressor gene but also with the appearance of microsatellite instability [18], and the involvement of mismatch repair genes such as *MGMT*, *BRCA1*, and *MLH1* in both familial and sporadic types of colon cancer [19, 20]. Ho K.R. and Vogelstein B. believed that the following disorders are necessary for the development of malignant tumors: mutational activation of oncogenes paired with inactivation of suppressor genes, mutations in at least four to five genes, and/or genetic alterations in genes associated with the tumor development [21].

A more recent model is the "non-genotoxic model". It focuses on important modulators of cancer risk, such as hormones, insulin resistance, diet, chemicals, obesity, *etc.* [22–24]. At first glance, these effects are not related to structural changes in DNA, but rather affect through functional aberrations, including epigenetic changes and alterations. The mathematical model of this theory is the two-stage model of clonal expansion by Moolgavkar S. [25]. According to this model, normal stem cells can be transformed by the first stochastic event (the first mutation) into intermediate cell forms, which in subsequent divisions give rise to intermediate cells that either die or differentiate. In addition, these intermediate cells can give rise to more intermediate cells, some of which can transform into malignant cells after a second stochastic event (mutation). These malignant cells can turn into a tumor after a certain period of time (delay).

Non-genotoxic model partially overlaps with the so-called Darwinian model of carcinogenesis. It is based on Novak's mathematical model and postulates that cellular selection, in addition to the resulting somatic mutations, is the driving force behind carcinogenesis [26, 27]. It is believed that the previous three qua-

si-mechanical types of models: the multistage model of Armitage and Doll [5, 6], the two-mutation model of Moolgavkar, Venson, and Knudson [28, 29], the multistage generalizing model of Little [30], and the models generalized on their basis that takes into account the effects of transmissible genomic instability [31–33], are based primarily on the hypothesis of Darwinian somatic evolution [34] whereas a truly evolutionary approach to cancer and its function in the population was proposed by Lichtenstein A. [35]. Carcinogenesis is seen as an evolutionarily conservative phenomenon — a programmed death of an organism. It is assumed that cancer has an important altruistic function: as a mediator of negative selection, it serves to preserve the integrity of the species gene pool and mediates its evolutionary adaptation [36].

Based on the model of clonal evolution and the assumption that the vast majority of tumor cells is capable of spreading and stimulating tumor growth, the goal of cancer treatment traditionally was to kill all cancer cells. This theory has recently been challenged by the cancer stem cell hypothesis, which postulates the existence of a rare population of tumor cells that have stem cell characteristics and are responsible for tumor growth, resistance, and recurrence. The evidence of cancer stem cell prediction has been described for breast, prostate, lung, intestinal, pancreatic, liver, and brain cancers [37–39].

The fifth type is a model of «tissue organization». It is more recent than the previously described models. It focuses on the microenvironment of tumors. The model has two aspects of basic research: the first part is the microenvironment [40, 41], and the second part is based on the theory of morphostats/morphostasis [42–44]. By analogy with the embryonic development, where morphogenetic fields organize tissue morphology, the morphostatic fields support normal cell behavior and tissue microarchitecture in the adult body. The most well-known sign of cancer is a violation of the tissue microarchitecture. Moreover, the appearance of cancer is more likely between different morphostatic fields or when morphostatic influence is disturbed (metaplasia) [43, 45].

The appearance of focal proliferative lesions can act as a precursor to the development of cancer. It is becoming increasingly clear that the occurrence of such lesions is not a cell-autonomous phenomenon, but depends on the microenvironmental signals received from surrounding cells and tissues [40]. The result is a change in tissue architecture, which translates into the emergence of a unique tumor microenvironment within these lesions associated with altered blood vessels or blood flow, which in turn can cause biochemical and metabolic changes that promote tumor progression [41].

The factors and signals that lead to disruption of tissue architecture are morphostats that diffuse through the tissue to determine cell phenotype and maintain tissue architecture and are the indicators of disruption of interactions between the stroma and epithelium [45]. Morphostats are most likely derived from the stem and stromal cells surrounding the epithelium [43]. Computer modeling of the potential effect of morphostats on the cell renewal and tissue microarchitecture showed that the disruption of the morphostatic gradient in the stroma, without mutations in the

epithelium, can generate precursors of epithelial cancer [45]. This mathematical model is consistent with the possibility that genetic and epigenetic changes in tumors can occur after the formation of a clone of abnormal cells that arose as a result of the failure of morphostatic control of the microarchitecture of adult tissues [45]. Within this model, the tumor microenvironment cannot be considered simply as a new factor to be added to the already long list of signaling factors. The microenvironment is the physical and biochemical support of the morphogenetic field that leads epithelial cells to differentiation and phenotype transformation, according to certain rules that can be understood using a systematic biological approach [46].

The models of inflammation are closely related to the model of tissue organization [47]. The widely known fact that chronic inflammation creates prerequisites for the development of malignant tumors [48, 39, 50–52] and supports tumor progression [53, 54] is not just a hypothesis, but a theoretically and experimentally confirmed model that has recently been emphasized not only by clinicians but also by pharmacologists [55]. Among the factors that mediate inflammation are oxidative stress [56, 57] and hypoxia [53, 58, 59], microbiome alterations [48, 60–62] and oncogenic viruses [51, 63, 64], immune disorders [65–67] and pathological aging [68–70], and lifestyle features, including diet, physical activity, and chronic emotional stress [71–75]. Most of these factors have their own mechanisms of influence on the tumor development outside the inflammation model.

Scientists often compare and contrast two types of models that are considered basic but incompatible: the mutational model and the tissue organization model [76, 77], which we have just reviewed. Some authors have shown, based on the verification of two types of models on the basis of epistemological and experimental evidence, that the model of tissue organization convincingly explains carcinogenesis if the evolutionary context is taken into account and propose to abandon the outdated hypothesis of somatic mutations [78, 79]. There are reasons to criticize the mutational model as a theory that describes later events of carcinogenesis rather than the causes of its occurrence [80]. Other authors believe that it adequately describes the onset and manifestations of carcinogenesis, as well as the tissue organization model, because it demonstrate two different and compatible biological pathways of carcinogenesis [77]. This point of view is consistent with the existence of integrative approaches, and suggests that they have a higher epistemic value than two separate theories [81].

Experimental evidence can be found that supports and contradicts most of the well-known theories, but there is no single theory that unifies all these data and ideas. Numerous authors have identified the need to develop a systematic approach to cancer that reconciles and takes into account the already known models [82–85]. An integrated model is developed with the inclusion of the concepts and notions of “emergence”, “system”, “thermodynamics” and “chaos”, “functional unit of tissue”. The general principles of carcinogenesis allowed the existing theories to become compatible as alternative ones [86]. The authors propose twelve principles that define the “framework of carcinogenesis”. Principles 1–10 — contain

the basic concepts on which the system is built, the principles and conditions for the emergence of a tumor as a new system. Principle 11 addresses the basis of cancer progression. Principle 12 relates to the application of the framework to translational research. The carcinogenesis framework, according to the authors, brings together current paradigms, concepts, and evidence regarding carcinogenesis into a single framework that includes previously incompatible perspectives and ideas, such as the mutational model, tissue organization model, evolutionary model, inflammation model, and others [86].

We have reviewed the most well-known and widespread theories and models of carcinogenesis. They are the basis for understanding the mechanisms of cancer, the emergence of factors for metabolic disorders in cancer cells, and serve as paradigms for deeper study and research of various types of this disease, methods of early diagnosis, long-term prognosis, prevention and development of new treatments. But, unfortunately, clinicians rarely take them into account, guided by clinical manifestations and developed treatment protocols. Regardless of which model is correct, the cancer development involves all the aberrations described in various models, including genomic, epigenomic, transcriptomic, proteomic, metabolomic, microbiomic, and generalized systemic alterations of the organism.

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Ключові моделі та теорії канцерогенезу

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Представлено короткий огляд найбільш відомих семи типів моделей канцерогенезу. Серед них мутаційні моделі, моделі геномної нестабільності, негенотоксична модель, Дарвіновські моделі, модель тканинної організації, моделі запалення та інтегрована модель. Кожна модель має специфічні онкогенні чинники, які викликають певні типи онкологічних захворювань, мають власні механізми та базуються на певних математичних моделях.

Ключові слова: канцерогенез, моделі та гіпотези, онкогенні чинники, молекулярні механізми, генетичні та епігенетичні порушення, мутації, мікрооточення пухлин

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