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REVIEW

Carcinogenesis: Evolution of Concepts

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Abstract—Cancer is considered as an unintended consequence of internal imperfection of multicellular organisms: Darwinian evolution "does not foresee the future and does not plan for it", it is forced to handle only anything that it has at a given moment "at hand", which makes inevitable compromises and restrictions. In this case, there are a number of founding dogmas including mutagenesis as the main driving force of carcinogenesis; the environment as the main source of mutagenic effects; tumor monoclonality; cancer cell multistage transformation as Darwinian process of successive mutation–selection cycles. Recent discoveries complicate, supplement, and sometimes transform into an opposite fixed concepts. As a result, a new "image" of carcinogenesis is formed as a biological phenomenon whose conservation is indicative of its evolutionary utility.

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Two phases can be distinguished in carcinogenesis: the "preliminary" phase of latent intracellular changes preceding the emergence of tumor and evidently lasting during the whole life, and the phase of obvious clinical symptoms of tumor growth.

The first phase is characterized by accumulation of mutations in the genome, which step-by-step transform the cell. Fundamental processes (metabolism, respiration, division, apoptosis) result in mutagenesis and then in carcinogenesis. Thus, vital activity of an organism is accompanied by a parallel process of its "creeping into carcinogenesis". The rate of the latter, which defines the probability of tumor emergence in a given individual [1], depends on the balance of counteracting forces, mutagenesis (external and internal damaging factors), and antimutagenesis (systems of DNA repair and apoptosis). Extracellular control mechanisms, in particular, those of immune control, are not considered here [2]. In most cases this balance, significantly influenced by the genetic status of the organism (its important role in both pro-mutagenic and anti-mutagenic processes is considered [3]), is favorable—the "creeping into carcinogenesis" is so slow that there is not enough time to complete tumor formation during the individual's life (cancer is "forced out" from the life limits or, as is stated in the existing expression, "not everybody lives till his own cancer").

Abbreviations: CSC, cancer stem cells; ROS, reactive oxygen species.

However, a significant fraction of people (in developed countries approximately 20% of the population) lives to the phase of obvious clinical tumor symptoms. Evidently in these cases, such factors as genetic predisposition to tumor diseases (inborn defects of cell division, apoptosis, DNA repair genes, and various gene polymorphisms) as well as unfavorable external effects contribute to different extent to these processes [4]. The balance shift towards pro-mutagenic effects sometimes so accelerates carcinogenesis that cancer overtakes an individual already during his life (depending on the acceleration rate, in elderly or even at a young age).

Evolution of concepts concerning some phases of carcinogenesis is the subject of this review.

GENERAL THESES

Etiological factors. The history of Russian oncology still retains polemics between outstanding researchers L. A. Zilber and L. M. Shabad, adherents of viral and chemical theories of cancer origin, respectively. Both proved to be right (profound ideas, incompatible at first sight, are often complementary in reality) because chemical carcinogens and viruses are able to cause tumor diseases [3, 5]. Moreover, it appeared that this property is characteristic of many different genotoxic factors (i.e. able to damage DNA), such as ultraviolet and ionizing radiation, bacterial infection, and chronic inflammation.

As has become clear rather recently, mutagenic effects originate both from the external and (mainly) from the internal environment [6]. Cell division is associated with inevitable replication errors; metabolic processes and respiration are associated with accumulation of aggressive reactive oxygen species (ROS); telomere shortening coupled with cell division leads to chromosomal aberrations; spontaneous processes of DNA depurination and methylcytosine deamination bring about DNA damage; and phagocytosis of apoptotic bodies is associated with large-scale natural transfection [7]. Although the "external" component of mutagenesis gives a way to a certain correction and therefore is an important object of prophylactic measures, the possibilities to influence the "internal" component are now extremely low.

Infectious agents. There is the widespread opinion that "cancer is not infectious". In most cases this is really so. Nevertheless, a significant fraction (15-20%) of malignant tumors is of viral origin [5]: under certain conditions infection of an individual by papilloma, hepatitis, Epstein–Barr, and some other viruses may cause a tumor disease.

Along with cases when virus is an infectious agent, sometimes a cancer cell itself is such an agent. As is proved by methods of genetic analysis, transmissible venereal sarcoma of dogs and transmissible cancer of "Tasmanian devil" (a marsupial beast, resident of Australia) are (rather rare) cases, when descendants of a tumor cell, that emerged long ago, maintain for ages the existence of a tumor clone by "jumping" from one individual to another (during sex contact or upon bites during fights) [8]. The cancer cell infectivity in humans can be revealed as a result of transplacental transmission (from mother to fetus) and organ transplantation, when unlimited division of a cryptic transformed donor cell begins under conditions of suppressed immunity.

Monoclonal origin. A tumor originates from a single transformed cell and therefore is its clone. This idea emerged owing to the intuitive belief that horizontal transfer of genetic information is impossible, in other words, the cancer cell is not able to pass its infectious agent to neighboring cells. This appeared to be incorrect (horizontal transfer is possible and evidently plays an important role in carcinogenesis [7, 9]). Nevertheless, the idea of monoclonal tumor origin resisted due to experimental support. Reconstruction of tumor "genealogical tree" has recently shown in a model system its origin from a single progenitor cell [10].

Tumor monoclonality at the moment of its emergence does not exclude its future clonal heterogeneity: genetic instability inherent to cancer cells constantly generates new clones. Moreover, "cancer underground", serving as the basement for tumor growth (see below), is evidently able to "replenish" it with newly transformed cells [11].

Mutagenesis and epigenesis. For a long time two ideas, "cancer is a disease of genes" and "cancer is a disease of gene regulation", opposed each other. According to the first idea, the cause of cancer is gene mutations, while according to the second these are epigenetic alterations (i.e. those involving systems of gene activity control). These views, also formerly considered as alternative, now mutually supplement each other: it appeared that there are two components in carcinogenesis—mutagenesis (point mutations, deletions, insertions, and chromosomal aberrations) [12, 13] and epigenesis (methylation of suppressor gene promoters, global genome demethylation, histone modifications, microRNA regulation) [14-18]. Thus, one would think that incompatible principles, chaotic (mutagenesis) and highly ordered (epigenetics), are getting on within the frames of carcinogenesis. Mutations are rare, random, and emerge in single cells (monoclonal). Epigenetic events, on the contrary, are put in order, they take the genome in and coordinate a number of complex subsystems, they are formed in embryogenesis and display themselves during subsequent life [19-25]. Epigenetic imprints leading to cancer are inheritable [26], emerge early [27], often at the stage of preclinical changes [28, 29], simultaneously in many cells (polyclonal) [30], and have deterministic character [31-33]. Methylation of some suppressor gene promoters during cancer transformation is not a chance but a regularity imprinted in the cell genome [34]. Complex coordination of epigenetic processes makes doubtful their stochastic nature and suggests, on the contrary, their deterministic character [15, 22].

The more ponderable are data in favor of an important role of each of two carcinogenesis components, the more acute is the problem of their relationships: what is primary and plays the main role and what is secondary. The solution to this problem will allow one to make clear whether cancer is random or regular. Actually, the opinion, that just mutagenesis leads to cancer, has dominated to the present time and suggests random character of mutagenesis. However, in connection with current reappraisal of values ("epigenetics wins over genetics" [14]) there appears feeling of this phenomenon's pre-determination.

Concept of cancer stem cell. Identification of cancer stem cells (CSC) [35] is a strong stimulus for revision of existing concepts of carcinogenesis. As was repeatedly noted, the CSC concept goes back to the 150-year-old "embryonal rest" theory of Virchow and Cohnheim, according to which cancer originates from "lost" embryonic cells present in an adult organism, usually dormant but able to wake up in response to inflammation [17, 36, 37]. In its modern form, the CSC concept is opposed to the widespread view of a tumor as a chaotic cell conglomerate and suggests, on the contrary, its hierarchic design. The tumor basis is represented by a small subpopulation of stem cells exhibiting a number of key properties like (i) the ability of self-renewal and differentiation (that is achieved by asymmetrical division resulting in the

maternal cell replacement by one daughter cell, "renewing" the maternal one, whereas the second daughter cell leaves for differentiation); (ii) plasticity (the ability to develop in different directions); (iii) an unlimited division potential; (iv) the ability to form tumor *de novo*. Stem cells probably make up a percentage of the cell population, though sometimes their content may be higher [38, 39] and can vary in tumors of various origin [40]. However, the main part of a tumor consists of differentiated cells that are doomed to final death and are not able to restore tumor *de novo*, but they dominate quantitatively and specify clinically the disease [41, 42].

Carcinogenesis as a variant of differentiation. The CSC concept is important in many aspects. In particular it makes it possible to explain difficulties of the present-day chemotherapy and to set new targets for it [43]. Besides, it stimulates reinterpretation of the key term in oncology – "transformation". Being superficially descriptive (and empty in essence), this term reflects the situation of the time of its emergence, namely, the absence of knowledge about the mechanism of carcinogenesis. Now much is known and the term "cancer differentiation", more rich in content, may come to take the place of hazy "transformation".

Not so much semantics as carcinogenesis is implied. Since the determination "stem" itself suggests the existence in a cell of differentiation ability (as a matter of fact, the cell is earmarked just for this), identification of a "cancer analog" of normal stem cell leads to a corresponding interpretation. Namely, carcinogenesis is not the "disease of differentiation" as is assumed, but rather a kind of differentiation, similar to "normal" in key aspects:

– the existence of progenitor cells (cancer stem cells);

– their plasticity suggesting choosing one of several possible variants of development;

– predestination of the pathway when the choice is over;

– formation of specialized tissue or organ.

As for the latter, the tumor quite corresponds to formal determination of the organ as an anatomically discrete complex of tissues integrated into the whole for carrying out specific functions [44], and it has appropriate attributes like hierarchic structure, often mimicking normal tissue structure [45], cell specialization [46], structure–functional unity with microenvironment [47], diverse inter-organ links [48], and invariable function of the organism's self-elimination [49].

Irrespective of CSC origin (directly from normal stem cells or from those originally more differentiated, but which later again acquired properties of stem cells [40, 45, 50, 51]), the fact of their existence itself is in favor of Virchow's ideas. It is possible that cancer progenitor cells [30], intended just for this (malignant) variant of development, are really initially present in the organism. Being for a long time under "expectation regime", they undergo constant influence of mutagens, which results in gradual erosion of the "restrain and counterbalance" system (protooncogenes and genes suppressors) and finally in activation of "cancer differentiation". In this model, "distribution of responsibilities" between mutagenesis and epigenetics looks as follows: the first serves as the multistage trigger of the "cancer differentiation" program, whereas the second serves as its realization mechanism [52].

There is evidence in favor of such interpretation. Normal and cancer stem cells exhibit a striking similarity, both being characterized by plasticity, asymmetrical division, unlimited proliferation, and activity of main regulators of embryonic development [17, 51, 53, 54]. The transcription module specific of embryonic stem cells appeared to be also activated in many cancer cells [55]. According to the "epigenetic progenitor model", cancer originates from stem cells that have undergone a number of epigenetic transformations, this background making it possible to reveal subsequent mutations [16, 30]. Early epigenetic events are responsible for the cell addiction to oncogenesis and predispose them to accumulation of corresponding mutations [15]. Being repelled from Virchow's thesis that "tumors grow in accordance with the same laws that regulate embryonic development", authors of a recent work cleared up extensive material regarding to what extent transcriptomes of tumor and developing tissue resemble each other, and they detected common global trends in their gene expression [56].

There are probably bifurcations in the differentiation pathways that direct cell differentiation along predetermined trajectories towards alternative states, to normal and cancer phenotypes. Thus, the clone of precancerous stem cells is capable of benign and malignant differentiation depending on existing conditions [57]. The extent of the stem cell association with the niche influences the balance between alternative pathways of development [51, 58, 59]. Mutations, inflammation, and some other factors weaken this association and promote choosing the "cancer" branch in development. Actually, visualization in real time of the hematopoietic progenitor cell division made it possible to identify symmetrical and asymmetrical divisions and to show that balance between them is shifted in response to different endogenous and exogenous factors, in particular to oncoproteins [60]. In this connection, the classical work by B. Mintz and K. Illmensee should be especially distinguished, in which they discovered totipotency of tumor cells and their ability to switch, depending on conditions, from one pathway of development to the other [61].

During its development a cancer cell co-opts standard ready-to-use functional modules such as epithelial–mesenchymal transition [62], aerobic glycolysis [63], angiogenic switch [64], escape from immune control, and immunity inhibition [65]. A characteristic property of

many tumors is expression of C/T (cancer/testis) antigens [66]. This peculiarity is considered as evidence of awakening in cancer cells of a transcription program inherent for embryonic cells and forming the standard malignant phenotype (immortality, immune invulnerability, invasiveness and metastasis, genome hypomethylation) [67].

LATENT PHASE OF CARCINOGENESIS

The "underground" for following growth of cancer is enlarged during this phase. As mentioned above, cell division is coupled with mutagenesis (replication errors, fixation of earlier defects). The μ-value (mutation rate per gene and cell division) may vary over a wide range [68], but already its existence and non-zero values are evidence of this intimate link. Active proliferation characteristic of large organisms with continuous self-renewal of their tissues therefore inevitably leads to emergence of cells progressing step-by-step along phases of transformation (here "transformation" is used as the term, although not quite adequate it is generally accepted). Complete transformation of one of them is only a matter of time.

The "underground" appears in the form of a growing "mutation pyramid" in which cells with the lowest number of "cancer" mutations are in the basement and those with the highest number of such mutations are at the top [49]. This pyramid grows in breadth and upwards till emergence at the top of it of a completely transformed cell that surmounted all barriers and was able to give rise to a tumor. The latter, being monoclonal at the initial step, as a rule, becomes polyclonal with time. This is stimulated by two situations: first, the cancer cell genetic instability giving rise to new clones and second the ability of "cancer underground" to replenish continuously the tumor with newly transformed cells [11]. In this way the most important tumor property (clonal heterogeneity) is formed, which creates the basis of its following progression.

The inevitable presence in each solid tumor of "its own underground", following from general considerations, is supported both by clinical observations ("each cancer has its own precancer" [69]) and by experimental data (the existence around tumor of broad "fields of cancerization" from genetically transformed cells, not revealed by routine methods, was shown [70]). This situation has clinical consequences. Surgery usually removes tumor, but not always the same happens with its "underground" (there are no practically acceptable methods for determination of borders of the latter), which is fraught with relapses. Besides, the "underground" creates special problems for application of chemotherapeutic treatment aimed at DNA damage. As mutagens, they may contribute to enhanced transformation of surviving cells of the "underground" and, as a result, to relapse.

Probably mutagenesis involves all cells of the organism, which means that in every tissue and organ there is its own growing "mutation pyramid". All participants of this "running along parallel paths" are directed to finish, but the "winner" is unpredictable (there are too many attendant circumstances influencing the result of the "race"). Such interpretation of the latent phase of carcinogenesis suggests tumor localization as random and its emergence as regular (due to continuous and progressive mutagenesis). It is in agreement with the remote observation called "the effect of communicating vessels" (Yu. I. Lorie), namely, lowering the number of cases of any single form of cancer as a rule is not accompanied by the same decrease in the general cancer incidence (other forms fill in the formed "niche"). Thus, despite success in oncology, mortality caused by cancer in the USA during the past 50 years practically did not change (from 193.9 cases per 100,000 population in 1952 to 193.4 cases in 2002).

Although it would seem that cancer is inevitable, not quite everybody comes into collision with it during the lifetime. There is no contradiction in this case. This is explained by the mortality caused by other factors (in particular, cardiovascular diseases revealed 296.1 cases per 100,000 population in 2002).

TUMOR PROGRESSION: DRIVING FORCES

It is assumed that the emerged tumor makes progress in accordance with laws of Darwinian evolution. Clones that form it compete for space and resources. The clone of cells, most viable, aggressive, and "evasive" with regard to chemotherapeutic preparations, wins at each turn of competitive struggle. The clone competition defines continuous tumor drift towards more pronounced malignant phenotype.

However, recently it has become obvious that this description does not explain everything and relationships within tumor are not restricted to the competition. The intercellular cooperation, repeatedly increasing oncogenic potential, also plays an important role [48]. One of its forms is horizontal transfer of genetic information. In particular, it is shown that phagocytosis of apoptotic bodies (as a matter of fact, the large-scale and continuous transfection *in vivo*) is a significant factor of mutagenesis and carcinogenesis [7, 71]. Another method is cell fusion (the widespread biological phenomenon that plays an important role in fertilization, tissue regeneration, and formation of placenta, muscle, and bone tissues [50, 72]). Cell fusion is probably also involved in carcinogenesis [73]. The fusion of migrating cells (macrophages, bone marrow cells) with tumor cells provides the latter with metastasis ability [74]. Tumor cell fusion with a normal stem cell may serve as the mechanism of emergence of a cancer stem cell [50].

Another kind of intercellular cooperation is exchange by secreted products. Tumor cells secrete into the environment multiple biologically active compounds (cytokines and chemokines [75, 76]) that give rise to mutually advantageous "barter". Thus, both the tumor cell itself and its neighbors gain from the acquirement by the tumor cell of the ability to secrete into the intercellular medium of some angiogenic or growth-stimulating factor. This kind of cooperation contributes to the cell specialization and possibly makes not quite obligatory all stages of cell transformation: this pathway may be just partial and following its special "trajectory". So, "malignancy" may be an integral property of the cell population rather than of an individual cell [46].

TUMOR AND ORGANISM

The tumor and organism relationships are intuitively (perhaps by analogy with infections) perceived as antagonistic. It seems that this does not correspond to reality. If tumor elimination were the real priority of the "host", it would be simply enough to ignore it. Most likely, the organism not only does not struggle against tumor, but on the contrary, it helps the tumor in all possible ways and the tumor exists exclusively due to the support from the immediately surrounding [44, 47, 76] and remote [77-85] normal tissues. Fibroblasts [86-88], tumor-associated macrophages [89-91], tumor-infiltrating neutrophils [92], stroma [47], bone marrow [82], and remote organs [79] are involved in the "escape action". Inflammation cells are an obligatory growth-stimulating component of a tumor focus [37, 75, 93]. Owing to the help from the outside, tumor cells get blood supply, grow, form metastases, and mutate at a higher rate [91, 94]. In response to the tumor-produced granulocyte colony-stimulating factor, synthesis in bone marrow of angiogenic peptide Bv8 increases, and as a result, myeloid cells are mobilized and rush to the tumor focus where they induce angiogenesis [95].

The ability of stromal fibroblasts to generate tracks in extracellular matrix and serve as a leader for epithelial cells following after was found in model experiments on cell invasion [96]. Specialized cells of remote organs (bone marrow, lymph nodes, lungs) are involved in formation of a pre-metastasis niche [79-81, 97, 98], later inhabited by metastasizing cells. Cytokines secreted by the microenvironment help cancer cells to escape drug action [84]. Complex relationships of normal and tumor cells result in formation of numerous "vicious circles", stimulating tumor progression. Although microenvironment factors sometimes exhibit "yin–yang" activity, i.e. depending on circumstances they can be either pro- or anti-carcinogenic [99], total balance is always formed in favor of growing tumor.

The immune system, the main protector against various invasions, plays a dual role in carcinogenesis. At initial steps, immunity is able to eliminate mutant cells and maintain for some time the balance ("to keep in check" transformed cells and make their expansion inadmissible) [100]. However, after appearance of clonal escape and tumor formation, the immune system stimulates development of the latter in a paradoxical way [93, 101, 102].

Thus, it is clear that tumor tissue is integrated in the complex network of intra-and inter-tissue interactions and that the development of tumor tissue is the result of collective efforts [103, 104]. As a result, the tumor process appears as a comprehensive program of systemic collapse.

KILLER FUNCTION OF CANCER

Cancer and organism death are so indissolubly associated in our consciousness that one seems a natural consequence of the other (metastasizing, in particular, is considered as a clear explanation of fatal end). However, ascertaining the cause-and-effect relationship is not its explanation. At the present time there is no explanation of causes and mechanisms of the tumor patient death, although just this may be the main aim of cancer studies. Special interest in the problem is generated by the evidence of broad involvement in this suicidal process of normal cell elements (see above). There arise many questions that still have no answers. Why is death inevitable (it would seem that there is no obvious necessity)? Is it a side result of tumor growth, the result of a local effect on normal tissues? Or, on the contrary, is the death predetermined, caused by some specific activity of a cancer cell, and "useful", and just owing to this it is so evolutionarily conserved?

Some issues are in favor of special properties of cancer.

It would seem that formation *de novo* of a small (in the range of tens-to-hundreds of grams) additional mass of cells should not have fatal consequences, like in the case of benign tumors. Inevitable death of a tumor patient, independently of the malignant tumor type and localization, suggests the existence in this tumor of a specific "killer" function [105] that, due to its universality, should be joined to other hallmarks of cancer [106].

Clinical observations show the ability of a tumor to exert generalized effects on an organism. Its local manifestations like brain compression, profuse hemorrhage, obturation of intestines, its perforation, etc. are fatal relatively rarely. More often localization of tumor and metastases are "neutral" in principle and do not obviously interfere in carrying out vital functions (like in the case of bone metastases of prostate cancer). Quite often, especially at early stages, there are no local signs of malignancy, but generalized paraneoplastic syndromes are prevalent such as anemia, coagulopathy, cachexia, anorexia, neuropathy, retinopathy, indisposition, weakness, hypoalbuminemia, hypercalcemia, hyponatremia, hypo-

glycemia, elevated temperature, and pathological alterations of vascular, endocrine, skin, neuromuscular, and bone systems [107-114]. Long before diagnosis was established, progressive weight decrease is noticed in some patients [115, 116].

It is improbable that cancer cell is able to produce some toxins or in general to do something which normal cell cannot do at different stages of its development. Mammalian cells produce a great number of biologically active compounds (cytokines, chemokines, ROS, etc.). It can be supposed that cancer cells, possessing a usual set of effects, use them improperly: in not normal combinations and/or concentrations, inadequately to the time and/or place, which introduces "perturbations" in homeostasis incompatible with life. For example, the most significant particular case of killer function, cancer cachexia (cause of death in ~20% patients) is due to enhanced excretion by tumor cells of a number of biologically active compounds [107]. Cytokine MIC-1, produced by the tumor, acts indirectly via central mechanisms (in particular, via hypothalamus) and causes anorexia and weight loss [117]. The contribution to killer function of such exotic forms of cell interaction as cell competition, absorption, and cannibalism are also conceivable [118-121].

EVOLUTIONARY DESTINATION

Cancer is considered as a byproduct of the imperfection of the multicellular organism, the result of inability of Darwinian evolution to "foresee and plan the future", as well as of its choice restriction by what is "at hand" at a given moment [122]. Really, the emergence of a clone of migrating cells, able to divide without control, can be explained in this way. However, it is difficult to explain everything following, namely, the inevitable and determined character of death (it is not necessary in the frames of existing paradigm and its inevitability is not justified). Besides, certainly, variants that are "at hand" now changed during millions years of evolution, but cancer remained a constant and unchanged attribute of the animal world.

These considerations push one to a positive answer to the question: "Does cancer kill the individual and save the species?" [123], suggesting the existence in cancer of some function. This follows from evolutionary conservation of the phenomenon, on one side, and from its altruistic character, pointing to some population advantages, on the other [124]. Some hypotheses concerning the supposed advantages have something in common, namely, they distinguish in cancer an important ability to correct the gene pool of the population. Thus, it can be a regulator of mutagenesis level in embryonic cells [123], "an evolutionary department of technical control" during periods of rapid changes in the species morphology [125, 126], a population "guardian" preventing the mutant allele spreading in it [49, 52, 127].

Evidently, only hereditary cancer, i.e. that caused by germ line mutations (1-2% of total disease incidence), carries out its evolutionary destination. Hereditary forms are relatively scanty, which is quite understandable because mutations of gametes are rare in general, while those concerning cancer-associated genes are even rarer.

Judging by lethal effect in mice of cancer-associated gene "knock-out", these genes are included in the group of essential genes and as such they are an object of powerful stabilizing selection. Probably mutations of these genes are more harmful for the species viability than mutations of any other genes [128]. This supposition is supported both by results of computer simulation [129] and by data of population genetics concerning reverse correlation between penetrance of "cancer" alleles and their frequency in the population [130].

Cancer is mainly a disease of elderly people, which seemingly does not agree with its supposed role of the "gene pool guardian". Two explanations are possible in this respect. One of them is that here we are running into the manifestation of antagonistic pleiotropy [131-133], in which the program carrying out some important function in youth continues to act in old age despite its useless or even harm at this age. According to a widespread point of view, aging is a stochastic process and is beyond the zone of activity of evolutionary mechanisms.

However, a different view at aging and, accordingly, at cancer is also possible. Gerontology, like oncology, is a field of strict ideological confrontation between the theses "aging is a stochastic process" [131, 134] and "aging is a programmed process" [135]. Recently obtained results on the existence in a model system (*Caenorhabditis elegans*) of transcription program of aging agree with the latter point of view [136]. Therefore, it may be that in addition to its function of the population "attendant", cancer also serves as the executor of programmed senile death.

Now efforts of oncologists are directed exclusively at cancer cell destruction that, with the account of its high variability, is a complicated task. Daily practice confirms this. A clearer understanding of the programmed death mechanism could contribute to formation of principally different therapeutic strategy aimed at neutralization of the harmful effects of the cancer cell rather than at its elimination. This approach appeared to be efficient in model systems: antibodies to VEGFR1 and VEGFR2 inhibit formation of metastases in mice in which VEGFR1- and VEGFR2-positive bone marrow cells are involved in formation of a pre-metastatic niche [80]; antibodies to MIC-1 prevent cachexia in mice with prostate cancer xenografts [117]; antibodies to interleukin-23 enhance immune response and protect against chemical carcinogenesis [137]. Since killer function is probably characteristic only of cancer cells, its inhibition should not cause strong side effects—this "Achilles heel" of modern chemotherapy.

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