ISSN 1070-3632, Russian Journal of General Chemistry, 2010, Vol. 80, No. 7, pp. 1447–1454. © Pleiades Publishing, Ltd., 2010.
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Phenoptosis Hypothesis as a Concept of Evolutionary Oncology

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Received June 10, 2009

Abstract—The development of the idea about cancer as a programmed death of organisms (also called phenoptosis) has been presented in the paper. The conformity of tumor growth and death caused by cancer to criteria of programmed death, the significance of cancer for evolution and regulation of the number of mutations in the population of multicellular organisms have been argued. It has been shown that the phenoptosis concept can explain some unsolved problems of the basic and evolutionary oncology. Experimental approaches to the verification the phenoptosis hypothesis as applied to oncology have also been proposed.

DOI: 10.1134/S1070363210070406

Tumor growth is one of the serious age-related reasons of human and animal death [1]. Accoring to the classical medical biological paradigm, carcinogenesis, like aging, represents a damage (more specifically, a series of damages) of the regulatory systems of a cell and an organism, which is meaningless in terms of the existemce of a population and species but lethal for an individual.

The present work presents an alternative view of tumor growth as an independent tanatogenetic program formed over the course of evolution as a mechanism for maintaining genomic stability and retention of the adaptation of a population to environmental conditions. A question of what criteria should met by a pathologic process (especially when it leads to death) to be treated as the realization of a certain biological program is touched by the way.

Brief Historical Aspect

Speaking about prerequisites for the problem of tumor growth, we should first of all remember the works of Mechnikov [2], in which he came to a paradoxical, for that time, conclusion that a pathologic process, namely inflammation, can have an essential adaptive value, if it is considered from the philogenetic viewpoint. Extention of this conclusion to a different general biological process, viz. development of malignant neoplasms, was long considered impossible. The state of neither the evolution theory and population genetics nor the biology of tumor cell gave grounds for such an extention. And when biologists and pathologists made attempts to answer the question of the German pathologist R. Verhoeff "What is tumor in a general sense?" [3], they beleived that the evolutionary consequences of tumors are no more meaningful than a lethal mechanic trauma. These theories include the concepts of embryonic dystopia [4], misdirected regenerative process [5], atavistic adaptive reaction on environmental conditions [6], and evolutionary cellular resistance [7]. Slightly apart stand the Bernet's concept of immune surveillance [8], since tumor growth is inexplicitly considered as a factor driving natural selection in the evolution of the specific immunity system, and quite an unusual Kozlov's concept [9] considering tumor as a source of "excess cellular masses" necessary for activation of evolutionary new genes and development of new cytotypes.

Since 1970s, the view of many general biological phenomena has been radically revised. The discovery of programmed cell death [10] and development of concepts of programmed functioning of the immune system ("immune disarmament" and "saving a foreign in an own") [11] have slightly undermined the attitudes of organocentrism in the evolutionary biology. Finally, the the hypothesis of programmed death of the the whole organism (phenoptosis), advanced later [12–14] formed a theoretical basis for a variety of concepts of

programmed death of species as an evolutionary significant phenomenon. Based on this hypothesis and comparative oncology data, the author of the present review [15, 16] and Lichtenstein [17] have developed a concept of the role of tumor growth in controlling the genetic homeostasis at the population level. To be fair, we have to mention here the work of Sommer [18] who advanced views on carcinogenesis quite similar to the phenoptosis theory, and, moreover, they were reported before the general concept of programmed death of an organism had been developed.

Criteria for Relating a Biological Reaction to the Tanatogenetic Programs

Before proceeding to consideration of the phenoptic role of tumor growth, let us dwell on the question of how we can relate one or another pathologic process to evolutionally established programs. The recognition of the fact that a certain succession of events or a reaction in a live system inevitably occurs as a consequence of a trigger process, does not mean alone that here we deal with a target-oriented prorgam. We have to be particularly careful just with pathologic reactions, since they can be underlain by abnormal functioning of the physiological system, i.e. by a program destined by the evolution for quite different purposes. Thus, for exampe, vein thrombosis of lower limbs (in the case of thrombophlebitis or in long-term immobilized patients) with the subsequent detachment of thrombotic masses and death of the patient of pulmonary embolism demonstrates a wonderful and an extreme complexity of the process, starting with triggering the blood coagulation cascade and ending with the development of the cardiopulmonary reflex shock.

Amyloidosis is a pathologic process which arises from different reasons (long-term chronic inflammation, myeloma, or genetic protein exchange defects) and invoves deposition of special protein complexes in kidney glomerules and organ frameworks (which disturbs their functioning and death of the organism, most frequently from renal insufficiency), too, at first glance, can seem a manifestation of the tanatogenetic program. However, even a casual perusal makes it evident that here there is no any programmed biological phenomenon, and this conclusion follows from the assessment of the expediency criterion of such reaction which offers no advantages both to an individual and to a whole species.

At the same time, the expediency criterion establishes that other two pathologically quite important processes, namely inflammation and apoptosis (and certain other forms of cell death), are actually programmed in nature. In these cases, reactions causing damage and death of tissues and cells (and, sometimes, of the whole individual) develop. But here this is biologically justified, entailing elimination of undesirable tissue components or pathogens, which is useful for the survival of most individuals and a whole species.

A similar physiological phenomenon, organoptosis, involves the involution of organs in the metamorphosis of insect or amphibia larvae [13]. Either the death of bacteria or yeast at a high population density or genomic damage can hardly be considered a programmed event, were it not for its obvious purpose [19]. However, the programmed nature of death of single celled eucaryotes is much easier established due to the fact that their phenoptosis program is underlain by apoptosis whose biological essence is sufficiently well established.

Thus, we can recognize two clear criteria for relating a death (of cells, organs, or species) to programmed processes. (1) The presence of a special signaling system initiated by a certain triggering factor; therewith, the lack of damage of this system eleminates completely the tanatogenetic effect of this factor. Note that components of this system can be involved in other, non-tanatogenetic mechanisms; like, say, Cytochrome *c,* a component of the respiratory chain, which takes part in apoptosis. (2) Clear evidence showing that the tanatogenetic effect of the program provides adaptive advantages for survival (individual and population). Switching off the program should adversely affect the environmental adaptability. Biological expendiency here serves as indirect evidence for the fact that this tanatogenetic reaction might results from target-oriented selection (in other words, this is indeed a program). This criterion and its use to rule out false organismal adaptations have been considered in detail by Lyubishchev [20].

General Formulation of the Hypothesis of Carcinogenesis as a Particular Case of Phenoptosis

The carcinogenesis hypothesis suggests that tumor growth is an elimination mechanism that operates to kill an individual, when the number of mutations in the proliferating populations of its constituent cells reaches a certain level. Concurrent accumulation of mutations in somatic and generative (sex) cells allowed, over the

course of evolution, to "adapt" carcinogenesis as a mechanism for elimination from a population of individuals bearing a great number of mutant alleles and thus decreasing the stability and adaptive potential of the population.

The carcinogenesis hypothesis is based on two central postulates. First, there is a close correlation between the numbers of mutations accumulated in the course of ontogenesis in somatic cells and the number of mutations in sex cells. Second, tumor growth has a negative impact of the survivability of an individual, but is useful for a population, since the number of mutant alleles in the generative cells of individuals died pose threat for the population stability, i.e. tumor growth is an evolutionally useful process. This phenomenon is a particular case of the general Hamilton's rule of evolution [21]: Phenomena causing death of separate individuals will be maintained by natural selection if they bring benefits for the population as a whole. It is suggested that such mechanism may prove especially actual, if a population has experienced a mutagenic factor sharply exceeding the background level of mutagenesis (for example, radioactive radiation). In this case, the system maintaining the genetic homeostasis and operative both in somatic and in sex nuclei (DNA reparation, apoptosis, etc.) turns to be unable to manage a great number of cells containing mutations, most of which are negative in terms of survivability of individuals and populations [22].

As known, the system maintaining the genetic homeostasis of an individual species is constructed by the hierarchic principle: Cells with an inconsistent DNA reparation system (molecular level) are removed by apoptosis (cellular level), and if the latter fails, the killer function of immunocompetent cells comes into force [23] (tissue level). Therefore, the existence of a mechanism functioning at the population level and activated in cases where lower level regulatory mechanisms are damaged seems reasonable. The work of such mechanisms may have a great biological meaning. When it comes to the elimination of a part of a population with an increased mutational load, tumor growth prevents too fast morphofunctional changes (i.e. slows down evolution) which, having burst in most species (descendants of carriers of a great number of mutations in the generative cells), might adversely affect the adaptability of the whole population or even entail its extinction.

Probably, initially tumor growth arose as a result of neutral evolution (independent on the pressure of selection) and played no biological role, since it occurred rarely and possessed primarily local destructuring properties. This is the way that calicoblastic epitheliomas [24], tumors in lower Coelenterata in which real tumors develop for the first time, reveal themselves [25, 26]. Apparently, the suggested phenoptotic role tumor growth first acquired in shellfish and tubemakers, when a developed vascular system appeared, and tumors got able to form real "hematogenic" metastases [15], which sharply enhanced the tenetogenetic properties of malignant tumors, and the tumors themselves got much more frequent [27].

Tumor Growth as an Evolutionally Justified Mechanism for Elimination of Excess Mutations

Let us compare the above-formulated postulates with oncological facts, as well as the genetics of somatic cells and the population genetics of organisms, taking into account that the most important event leading to tumor development is the mutation process, and the most dramatic effect is a death of an individual. To this end, let us consider the following facts.

(1) The spectra of mutations and their effect on the survivability of somatic cells and organisms as a whole are generally quite similar. An exception is provided by aneuploids (cells with a changed number of chromosomes) whose selection in the populations of somatic cells is subject to complicated phase changes different from those characteristic of whole organisms [28]. Thus, both somatic and sex cells accumulate similar genomic damages.

(2) The frequencies of mutations in somatic and sex cells are similar. According to [29], the nondisjunction frequency for marker chromosomes in mouse marrow cells is equal to that for the X-chromosome in mammalian gametes during meiosis. With age, the frequency of generative and somatic mutations increases, in parallel with increasing probability of tumors [1, 30].

(3) Antimutagenic mechanisms responsible for genetic homeostasis in somatic and sex cells are similar in many respects. These primarily include DNA reparation and p53-dependent cell death. Note by the way that disorders in these mechanisms play an important role in carcinogenesis [31]. As to immunocompetent cells, then they do not control the homeostasis of genome gametes. True enough, their role in carcinogenesis and control of the genetic homeostasis of somatic cells have to be studied in more detail.

(4) Mutations in both gametes and somatic cells attain their significance at the population level. Mutations in generative cells are generally recessive (not developing) and accumulate in a population in the heterozygous state maintained by frequency-dependent selection [22]. Naturally, as the number of such heterozygotes in the population reachs a critical level depending on the probability of crossing of two individuals bearing unfavorable mutations in the same gene can produce numerous descendants with a decreased environmental adaptability. Further on genetic drift (or, according to Dubinin [22], genetic automatic processes) will lead to unfavorable changes in the gene pool of the whole population and initiate its biological regress. And the accumulation of mutant somatic cells will cause either general disadaptation, which occurs fairly rarely, for example, at a chronic radiation sickness, or tumor development, which occurs much more frequently and leads to death.

The aforesaid suggests a correlation between mutagenesis activity in generative cells and development of carcinogenesis from somatic cells. Let us show that such correlation can be evolutionally expedient. To this end, let us turn to comparative oncology.

(1) The rate of spontaneous tumors is a fairly definite species-specific characteristic, which implies a strong impact of the stabilizing natural selection by this criterion. Otherwise, a tendency would be observed to minimize this phenomenon unfavorable for the survival of an individual. However, as shown in [15], the tumor frequency distribution in the evolution series follows parallel evolution laws, i.e. no tendency for minimization is observed at all, even though certain species (guinea pigs, common ton, and some others), by still unclear reasons, have become relatively resistant to carcinogenesis over the course of evolution. Obviously, the mechanisms of this resistance are operative in different links of the hierarchic system, which controls genetic homeostasis at levels lower than population; however, this statement is still early to concretize. Strong evidence in favor or carcinogenesis expediency is provided by the evolutionary conservatism of this process developed already at the coelenterate level are undergone no essential changes, beginning with shelfish and ending with mammals [26].

(2) The rate of spontaneous tumors in species even prone to tumors is generally no higher than 10% [15], while animal strains highly prone to cancer diseases can be maintained exclusively by artificial selection; sometimes such strains completely extinguish because 100% of animals die of tumors. It is known that in the case of interspecies hybridization the progeny of certain fish can completely die of melanomas developed due to unbalanced gene regulation in the hybrid genome [32]. These facts provide clear evidence for the elimination potential of tumor growth.

(3) A sharp increase of the rates of human and animal tumor diseases falls on the age, when the reproductive function is still preserved, which implies accumulation of the mutational load in somatic cells.

(4) Lethal mutations implemented directly through tumor growth are known. Such mutations in lower animals cause, for example, Morgan-Stark №1 tumor in drosophilas, as we as tumors in lepidopterans Pipera nigra, which are inheritated as typical Mendel's X-linked traits and eliminate 100% of homozygous species at the larvae level [15, 33]. Similar tumors are known to occur in humans: retinoblastoma, tumors at the Li–Fraumeni, Fancony, and Wilms syndromes, xeroderma pigmentosum, familial polyposis of colon, etc. In all these cases, mutations in generative cells determinately and in a fairly early, not infrequently in the pre-reproductive ages, lead to death, and their significance as a factor of selection is undoubted.

(5) Analysis of the dynamics of the mutation process in somatic cells in view of the multistage nature of carcinogenesis raises a lot of questions. There are only rare cases, when only two mutations are enough for a tumor clone to form; more frequently, 5–6 or even 10–12 are required [34–36]. However, spontaneous mutagenesis cannot induce so many directed mutations in a single cell of a mammalian organism over the ontogenesis period. Moreover, instead of a seemingly logical correlation between body weight (cell number) and susceptibility to tumor, quite a different phenomenon is observed, which was given the name Peto's paradox [37]: Equal cumulative tumor rates in animals much differing from each other in body weights, like, for example, a mouse and a human. Further on, tumors develop in humans (and mice) with a probability of up to 10%, whereas the probability of malignant transformation depends on such rare events as gene mutations (10^{-7} per gene per division), and, therewith, their target represents less than 1% of the genome [17]. Consequently, tumors always appear at a slightly increased level of spontaneous mutagenesis. Not excluded the existence of a special phenoptotic program which induces directed mutagenesis in oncogenes,

probably, under the action of mutator genes, after a certain degree of genomic damage has been reached.

(6) It is also striking that damages in antimutagenic mechanisms not infrequently switch their function from antioncogenic to pro-oncogenic. It is quite possible that this switching, along with a harmonized set of aggressive properties of tumor cells, forms a part of the phenoptotic programs. The same also relates to the protein p53 [38], immune factors [39, 40], and, not excluded, DNA reparation. With respect to the the p53 protein, we can even make a slightly risky suggestion that it plays a key role in switching the elimination program, since it controls DNA reparation, activates apoptosis, possibly takes part (when the gene p53 is damaged) in the elimination of mutant cells with immune-competent cells, and favors tumor progression due to its transcriptional activity, i.e. is in fact involved in "switching on" phenoptosis.

(7) An attempt was made to assess the significance of tumor growth as a factor of the population homeostasis, by means of mathematical simulation. Computational analysis of the consequences of enhanced resistance to tumor growth in humans over 10^4 generations was performed. It was found that initially the rate of tumor-associated mortality tends to decline, but then the distribution of mutant alleles over the population starts to enhance, thereby inducing a considerable biological regress [41].

Together the above evidence suggests that the malignant cellular growth acts a factor of natural selection, and the species-specific rate of spontaneous tumors and, as a consequence, mutation level in gametes of the given species, are subject to evolutionary correction.

Let us return to the criteria of belonging to tenatogenetic programs, formulated in the beginning of the paper, as see whether tumor growth meets these conditions. Carcinogenesis is fully consistent with the first requirement: Tumor develops upon damage or disturbance of the epigenetic regulation of certain genes; further on tumor progression involves a great number of signal chains responsible for control over proliferation, cell death, angiogenesis (formation of vessels), locomotor phenotype, differentialtion, and immune response [42–48], with a wonderfully similar and equifinal (even though with certain variations depending on hystogenesis and localization) occurrence, but always leading to a lethal outcome for the tumor-carrier. Tumor forms its own stromal microenvironment and actively creates sites for future metastases (so-called metastatic niches) [49, 50]. A review of evidence for close cooperative interrelationships between tumors and tumor carrier organisms is given in [51].

However, it should be stressed that not all tumor progression phenomena and their interactions with host organism systems, even though they seem adaptive in nature, arose as a result of directed selection; some of them could be acquired over the course of neutral evolution. As example of such a neutral involvement into carcinogenesis is provided by numerous ABC proteins associated with multiple drug resistance of tumor cells (one of the most urgent problems of neoplasm chemotherapy). The fact that the ability of these cells to take part in carcinogenesis was acquired over the course of neutral evolution is evidenced by two instants: First, one hardly identifies a factor of selection by a trait that is actual for blastomas in natural conditions, and, second, there transport proteins are also functioning in normal stem cells [52].

Factors responsible for tumor-inducing mutations exert a direct lethal effect in doses much higher than carcinogenic ones. There are animal species and strains which rarely suffer of tumors, but the mechanism of carcinogenesis is impossible to "break" completely in view of the great number of its involved alternative pathways; defects in many of which exert an extremely unfavorable impact on functioning physiological systems and vitality of the organism.

The situation with the second criterion, i.e. biological expediency targeted at population survivability, is far not as satisfactory. There is sufficient indirect evidence showing that tumor growth is a manifestation of the operation of the biologically expedient phenoptotic program. However, no direct evidence is available to show that carcinogenesis more or less selectively eliminates just those individuals which have a high mutational load in the generative cells and that the lack of such elimination can aversely affect population existence. In our opinion, direct experimental verification of this hypothesis is possible (even though extremely labor-consuming). To this end, the following approaches can be used.

Possible Approaches to Experimental Verification of the Hypothesis of Tumor Growth as a Particular Case of Phenoptosis

A method for detecting mutations accumulated over the whole life [53, 54]. This method involves introduction into the mouse genome of a target gene

lacZ which is neutral in terms of cell vitality, and damages in this gene do not lead to cell death. The gene is taken off from a tissue sample taken by biopsy, cloned, and analyzed for mutations.

It is desirable that such gene is introduced in the genetype of a mouse line in which the rate of spontaneous tumors is close to a wild-type rate (10–30%). After that one should explore the dynamics of mutation accumulation in the generative cells, using sperma samples or bioptates of sex glands. The experiment is continued until natural death of mice, after which patomorphological examination for neoplasms is performed. If the suggestion about selective elimination of individuals bearing a great number of mutations is valid, then we can expect a strong correlation between the level of accumulated damages of the gene lacZ in the generative cells and the probability of tumor development. A similar research should be performed on a population of mice exposed to varied radiation doses.

To find out what is the significance for the population of that part of the mutational load, which is eliminated with animals died of blastoma, we recommend the following experimental scheme. Based on thorough observations on a sufficiently big nonlinear population, mice with tumors removed by surgery (skin, soft tissues, or breast tumors). The tumors are removed, the animals are crossed, and among descendants, again, a group is selected by the above criteria. The animals are maintained in conditions as-close-as possible to natural, such generations are produced many times, and the state and adaptability of the population are studied and compared with the wild type in terms of fertility, mortality terms, etc. For clearer effects, it is advisable to subject the experimental and control (no selection and tumor surgery) mouse populations to, for instance, ionizing radiation.

In our opinion, it is only positive results of such research that will allow the phenoptotic role of carcinogenesis to be considered as a fully established fact.

Differences Between Our and Lichtenstein's Hypotheses

The hypothesis of a possible role of tumors as a mechanism of elimination of excess mutational load, we presented here, coincides with the views presented by Lichtenstein in [17, 51]. At the same time, we would like to highlight the principal differences in our and Lichtenstein's view of the phenoptotic role of tumor growth. There are two issues to be dwelt on.

(1) We consider it unlikely and artificial to think that tumors possess some special "killer" mechanisms different from presently known mechanisms leading to death of people with malignant tumors, such as sepsis, bleeding, intoxication with degradation products, hepatargy caused by metastatic liver disease, and others, and, therewith, hematogenic metastases and their caused disorders most commonly lead to unfavorable disease outcomes (see, for example, [55]). On the other hand, the rarely metastasing basal cellular cancer can many years exist in patients, even though classical local malignancy manifestations take place. Moreover, a fast growing tumor tissue always contains extended necrotic niduses, and the resorption of necrotic masses from them causes intoxications and homeostatic disorders, including immune depression and coagulopathy (blood clotting disorder). Cytokines secreted by tumors and modulating the immune response to the side of stimulation of blastoma growth can induce immune failure and fatal infectious complications. However, this is likely to be a side effect rather than the main target of the secretory activity of tumor cells. It is well known in practical pathology from everyday experience with corpses of humans and experimental animals died of tumors опухолей that the death generally results from concrete and morphologically visualized reasons, and modern information on the physiology of tumor growth allows their quite adequate explanation. In this connection, there are no reasons to assume existence of an unknown "killer" mechanism for neoplasms.

(2) We can agree with the statement that research into the mechanisms of transformation resistance is an important field of comparative oncology, but suggest that the Lichtenstein's concept underestimates the role of higher level mechanisms of mutation elimination and antitumor surveillance. In our opinion, the interspecies differences in sensitivity to tumors are mainly underlain by a different efficiency of the elimination of cells with a damaged genome, rather than a different ability of cells to transformation. (This issue is far beyond the scope of the present paper and discussed in more detail in [56].)

CONCLUSIONS

Thus, in terms of the biological expediency, carcinogenesis is a process with a special phenoptotic mechanism, which provides population stability due to

negative selection of individuals with damaged genomes of somatic and generative cells. This process plays an important role in evolution: It controls the variability of the population and preserves its environmental adaptability. This concept of the evolutionary biological basis of tumor growth gives a satisfactory explanation of the evolutionary conservatism of the major antimutagenic mechanisms: DNA reparation and p53-induced cell death. This concept correlates the variability and tumor sensitivity of organisms, which explains the uneven distribution of tumor rates in different families inside vertebrate animal classes and the parallel nature of the evolution of this trait in different taxa. Clearly, these phenomena are explained by a different efficiency of control over somatic mutagenesis, and, therefore, evolutionally active species reached greater biological progress and genetic variability, undergo more somatic and generative mutations (as a necessary condition for evolution), and, as a consequence, more frequently suffer of spontaneous tumors [25–27].

However, we have to admit that this theoretically quite an attractive concept is still supported by indirect evidence only. Direct experimental verification of this hypothesis is undeniably an urgent task of research in this field.

Another practically important task is to find out the reasons why certain animal species (such as guinea pig) managed to minimize in the evolution process the species-specific rate of spontaneous tumors. Knowledge of these reasons will make it possible to find real approaches to controlling the tanatogenetic program of an organism, attained as tumor growth.

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