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Review Article

Oncology Section

The Generalised Mutation Theory of Oncogenesis

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ABSTRACT

Several theories of oncogenesis are known at present, the most accepted of which is the mutational theory. However, none of the theories explain the whole set of phenomena associated with the initiation and development of cancer. The aim of the review was to try to develop a consistent theory of oncogenesis which generalises and supplements some of the already known concepts of the essence of malignization processes in cells with the new developments by the authors in the field of oncogenesis. It was concluded that the evolutionary aspect of oncogenesis allows to find out the causes of biochemical changes in a malignant cell as well as the nature of chromomeres and their functions in oncogenesis. Among the most important results of the proposed review are the suggestions on the role of evolutionary factors, the role of the genome instability of the malignant cells and the role of chromomeres in these cells.

Keywords: Cell genome instability, Chromomeres, Genetic programs of cell functioning, Mutations, Oncogenesis, Reverse evolution, Stem cells

INTRODUCTION

The problem of cancer is elucidated in quite different ways in the surveys of scientists from various academic schools. The spectrum of questions on the causes and mechanisms of the origin of cancer is constantly expanding; however scientific answers on these questions are much less fundamental and unified. The only universally recognised scientific fact applies to the carcinogens and their role in the origin of cancer. Multiple environmental influences or factors can potentially be carcinogenic (may affect the genetic changes in the nucleus of the somatic cells). Among them psychogenics, infections, viruses, ionizing radiation, intoxication as a result of pathogenetic chemical effects, smoking, alcoholization, food and inhalation poisoning, etc., take place. The second group of factors includes endogenous disorders of the homeostasis of the body such as stress, hypoxia, the presence and accumulation of genetic mutations leading to disorders in the DNA replication system, dysmetabolic and endocrine disorders, etc.

Nevertheless, scientifically reflected points of view on the problem are significantly different concerning the problems of origin of cancer and other malignant tumours. Several theories of carcinogenesis are currently distinguished in modern oncology, but the main and generally accepted is the mutational theory. According to the theory, cancer (malignant neoplasms) develops from a single tumour cell. According to this statement, cancer in the human body arises because of the accumulation of mutations in specific sites of cellular DNA. This leads to the formation of defective proteins. The founder of the theory is the German biologist Teodor Boveri, professor of the University of Wurzburg. In 1914, he suggested that chromosomal abnormalities could lead to cancer. Subsequently, these violations were qualified as mutations. From the 60s of the last century, the concept of mutagenesis was formulated as the main cause of the development of tumours in oncology and fundamental sciences researching the biology of cancer. Hence, the mutational theory is the most justified now-a-days [1-5]. However, none of the previously proposed theories of oncogenesis, including the present mutational theory explains the totality of phenomena associated with the initiation and development of cancer. This paper attempts in creating a consistent theory of oncogenesis, combining some of the already known concepts, as well as our new developments of the problem under discussion.

Literature Review

The role of mutations and instability of the genome in the process of oncogenesis: In our previous works on the mathematical modeling of carcinogenesis [6,7], the possibility of cell malignancy of various species was assumed. At present, such representations are recognized as erroneous. The proposed new theory uses the notion that only stem cells can be malignant [1,2], and the cause of malignancy is the damage (most often-the mutational nature) of some genes, namely, suppressor genes and genes that does DNA repair. The damage of some of these genes in the cell causes the instability of the genome and is the first step towards its malignancy [8-13].

Mutations can arise due to both external (e.g., exposure to ionizing radiation) and internal factors.

As for internal factors, as known, with each division of the cell a mutation can occur in this cell with a certain probability. Thus, the more often the cell divides, the more likely mutations can occur, including in those genes that must ensure the stability of the genome.

It is important to note that at conception, the initial genotype of an arbitrarily chosen individual can contain a different number of both functional (undamaged) genes and genes damaged by mutations (afunctional) responsible for the stability of the genome. It follows that the less functional (undamaged) genes the individual has in the genome from those that ensure the stability of the genome, the earlier the instability of the genome will occur, the malignancy process of any stem cell of the individual will begin. This, in particular, explains the risk of oncological disease in childhood and even in the foetus, since parents can be the carriers of those afunctional genes that normally are responsible for the stability of the genome.

The evolutionary aspect of the problem and the role of chromomeres: Why the instability of the cell genome lead to the malignancy of this cell? In our opinion, to understand this issue, we need to discuss some evolutionary aspects of the problem and find out what role is played by chromomeres in the processes under consideration and by introns in cells.

Nature usually rejects the unnecessary. At the same time, chromomeres make up about 90% of the chromatin of the cell and this part of the chromatin is not used by the cell [14-16]. Then what is the role of chromomeres? It can be assumed that chromomeres

contain genetic information that is not used by the cell now, but was used before.

It is believed that the processes of evolutionary transformation of ancestral species into new species occurred through the appearance of such mutations that blocked the development of ancestral species (most often in the juvenile stage of development) and led to the emergence of new (subsidiary) species possessing new properties [17].

It is believed that with each sequential blocking of the genetic program of ancestral species in the cell, a chromomer was created containing the genetic information (genetic program) of this ancestral species, and the cell itself proceeded to work on a new genetic program.

Apparently, the same applies to introns in cells, if it is assumed that the exons contain the genetic information used by the cell, and introns contain those DNA cell fragments that are not normally used by this cell.

As cell divides, the errors as well as the DNA damage of these cells can occur with some probability, although the probability of these errors and damages in the normal state might be low. In the normal state, the vast majority of these errors and damages are corrected or eliminated by the cell. However, in conditions of the instability of the cell genome, the number of uncured damages steadily increase and the genetic program by which the cell worked, quickly enough appears first damaged, and then completely destroyed.

It is believed that the consequence of destruction of the previously working genetic program can be both cell death and the unblocking of the genetic program that remained from the previous (ancestral) species and is recorded in one of chromomeres.

It is assumed that in this case, after the initial genetic program has been destroyed, the cell starts working according to the program of this ancestral species. If, due to the instability of the genome, this genetic program is destroyed, the cell will move to work on the genetic program of the cell, which evolutionarily preceded the previous one.

Reverse evolution: Thus, the transformation process of malignant cells can be characterised as a process of reverse evolution (involution). In other words, for a malignant cell, continuous sequential changes in genetic programs are characteristic, according to which the cell functions from the currently existing to the increasingly ancient.

It is clear that the change in genetic programs used by cells determines both the functions, and the morphological and biochemical characteristics of the transformed cells. In particular, cytokines and other substances that correspond to the ancestral form should appear in the transforming cell, and the cell starts to leave the biochemical control of the organism and transform more and more strongly [8,13].

What kind of Transformation should this be?

If we proceed from the concept of oncogenesis as a process of reverse evolution, it is necessary to take into account the physicochemical features of the habitat of organisms, especially in ancient times. We recall these features. As known, life originated in the oceans in an oxygen-free environment. The use of oxygen by organisms became possible only after its content in the oceans reached the Pasteur point, i.e., the concentration of oxygen equals to 1.59 mmHg. It is believed to have occured in the time interval from 620 million to 1,000 million years ago – at the beginning of the Cambrian or at the end of the Proterozoic. This view is supported by the fact that in the Proterozoic there were (according to modern ideas) only or mostly unicellular organisms, and in the Cambrian an explosion of speciation occurred and multicellular organisms began to appear in large numbers [17]. Thus, the most ancient organisms were anaerobes, and oxygen was a poison for them or, at least, a harmful substance.

How is it related to the above considerations? Let us discuss some known facts concerning the changes observed in oncogenesis.

In the transformation process of tumour cells, a set of hormonal and other specific receptors can change on their surface. It is known [8-11] that the oncological process initially changes the biochemical properties of cells that have lost normal differentiation, and biochemical anaplasia of tumours causes a number of metabolism features that distinguish them from normal tissues. The tumour tissue is rich in cholesterol, glycogen, and nucleic acids. In the tumour tissue, glycolytic processes predominate over oxidative processes; there are few aerobic systems (cytochrome oxidase and catalase). Expressed glycolytic processes are accompanied by the accumulation of lactic acid in the tissue. The cell is dominated by the phenomenon of anaerobic glycolysis. The negative Pasteur effect is observed.

In tumour cells, the area of contacts that ensure the adhesiveness of cell membranes decreases. Embryonic proteins that are not native to mature cells begin to be synthesized in the cell. Tumours tend to simplify the protein composition compared to the mature cell. Formed tumour lives in a hypoxic state. The blood flow in tumour does not exceed 15% of the normal blood flow (usually significantly less). Tumour actively uses glucose even under aerobic conditions. During starvation, tumour continues to multiply due to substances of other tissues. Significant changes are observed at the biochemical level.

These facts indicate that the development of tumours causes an increasingly anaerobic nature of biochemical processes in the cell.

Such are the literary data. However, precisely such phenomena should be observed in transforming cells, if we proceed from the concept of oncogenesis proposed in the present work as a process of reverse evolution!

There are many signs that distinguish normal cells from tumour cells in different stages of the disease. Therefore, neoplasia, perhaps, corresponds to the use of genetic programs by cells that existed in the days of ancient colonial organisms, and the genetic program of metastatic cells corresponds to the period of evolution, when, basically, the simplest unicellular organisms existed. Such views are confirmed by the fact that the tendency of metastases to migrate to hypoxic zones or tissue necrosis is known where there is little or no harmful oxygen for them [12]. It is also possible that metastatic cells bite into tissues and form ineffective vessels not in order to gain access to oxygen, but on the contrary, to minimise contact with it. However, these phenomena can also be related to the fact that among the oldest unicellular organisms (analogues of metastatic cells) there were both predators and saprophytes, eating everything possible.

At first glance, the proposed theory has a serious drawback due to the fact that reverse evolution caused by genomic instability would ultimately lead to the complete destruction of nucleotide sequences in transforming cells and the death of these cells. However, it should be remembered that in the process of reverse evolution at some instant, cells begin to function according to the programs of those ancestral species that were formed under anaerobic conditions, fundamentally different from modern ones. These organisms existed in an oxygen-free environment with a temperature of up to 50°C and were not protected by the ozone layer [12]. Therefore, the mechanisms ensuring the stability of the genomes of these early organisms were constructed in a fundamentally different way from modern ones, which allowed them to avoid the problems associated with the instability of the genome. If we proceed from the generally accepted hypothesis that all modern cells are organisms that became symbionts in olden times, and one of the groups of these symbionts (mitochondria) was capable of aerobic respiration,

it can be assumed that the present cells of metastases are cells in which an aerobic symbiont has died or does not function, while an anaerobic symbiont safely survives and functions.

Probably, such unicellular organisms were potentially immortal. It should be noted that if the metastasic cells are really analogues of these ancient cells, then oxygen must be a poison for them and the metastasized cells should strive to be in a medium with the least oxygen content, that is, in areas of hypoxic tissue necrosis. The results given in a number of works (e.g., [18-21]) confirm the existence of such a phenomenon.

Mechanism of tumourogenesis: The existing knowledge of these mechanisms is insufficient, and we again cannot do without the use of hypotheses.

At present, the main classification of stem cells is a classification by the criterion of their potency. It is assumed [22,23] that unipotent cells are incapable of malignantization. Perhaps this also applies to multipotent cells. However, the question of the relationship between the potency of stem cells and their ability to be malignant is not yet fully understood. In this regard, we call stem cells that can be malignant oncopotent cells. The next problem is that the connection between the hierarchy of stem cells and the degree of their direct participation in the elimination of various injuries is also not quite clear. At the same time, it seems natural that Oncopotent Cells (OPCs) that are most involved in the removal of damages are most likely to be malignant, since they most often perform fission.

Let us be more specific. Assume that in the area of any tissue there was a damage, which should be eliminated. In this case, a biochemical signal will be developed, and the nearest OPC will begin to actively divide, creating cells necessary to repair this damage (perhaps, these cells are capable of migration).

Nevertheless, no damage can be restored. In this case, a chronic process arises, which constantly generates signals going to the nearest OPC. In response, the nearest defense industry is divided repeatedly. However, the more fission the OPC produces, the more likely such a mutation will occur, which will damage one of the genes responsible for the stability of the genome. In addition, the more such genes are damaged, the more likely cell malignancy and carcinogenesis.

Consider, for example, the following situation. A very small piece of asbestos fell into the human respiratory system and stuck in the lung tissue. This piece traumatizes the tissue, and the body produces signals that cause the OPC to eliminate the defect.

To do this, the oncopotent cell (possibly-cells) commits divisions in order to eliminate the damage. However, the damage cannot be eliminated. Therefore, the OPC is divided repeatedly. This leads to an increase in the number of mutations in the OPC, then to the instability of its genome and the transformation of this cell into a Cancerous Stem Cell (CSC).

Let us consider another example. The emergence of cervical cancer is associated, as known, with the exposure of certain viruses. Such viruses, parasitizing in cervical cells, are introduced into these cells, ultimately destroying them. In itself, this does not pose a great threat to the body. However, if a cure does not occur, then a chronic process arises. As a result of this, as in the previous example, OPCs are often forced to divide to repair the damage caused by the viruses, which increases the probability of transformation of these OPCs into CSCs. The above examples substantiate the significance of chronic processes in oncogenesis.

The mechanism of carcinogenesis associated with the exposure to radiation is somewhat different. Ionizing radiation causes mutations in cells, which can lead to genomic instability and subsequent cell malignancy. The higher the dose of radiation the greater the probability of damage to genes that ensure the stability of the genome, and the lower the life expectancy on an average. However, irradiation is usually not a chronic one and after the cessation of this impact a person can live indefinitely, although the greater the dose of radiation, the smaller the average life span.

As for chemical carcinogenesis, the peculiarities of this process depend on whether the carcinogen can be excreted from the body or not. If it can be excreted, then the mechanism of the process under consideration is inherently similar to radiation carcinogenesis. If the carcinogen cannot be excreted, then this is an analogue of the chronic process discussed above.

Thus, the proposed theory is based on the notion that there are two main factors contributing to the onset of cancer. One of them is a sharp increase in the number of divisions of any OPC (most often, due to some pathological process). Another factor is the inherently small number of those genes that prevent the instability of the genome.

In particular, it can be assumed that the negative results of stem cell replenishment are associated with the use of cells obtained from those donors in whom a significant part of the genomes ensuring the stability of the genome were damaged during conception.

The authors of the article suggest that specialists will also be interested in discussing some issues that are indirectly related to the above theory of oncogenesis.

At the dawn of evolution in the context of an oxygen-free environment, the end product of the vital activity of unicellular organisms was, mainly lactate. With their intensive vital activity in an oxygen-free environment, lactate could accumulate in significant concentrations. At the same time, the normal course of life processes was limited by the fact that at extremely high concentrations of lactate, the direction of biochemical reactions could change, and this threatened ancient organisms with death. In connection with this, at high concentrations of lactate, ancient organisms probably limited their vital activity and metabolism to the maximum, and, one might say, died away.

Considering that such mechanisms were the most ancient, one can assume that they were the most universal. The foregoing allows us to suggest that lactate is a universal repressor of cell division.

Is it possible to use high concentrations of lactate for the therapy of malignant tumours instead of (or along with) other drugs? The question of using lactate for the purposes of antitumour therapy, to the best of our knowledge, has not been investigated, or has been little studied. Yet, it is known that the introduction of large doses of lactate into the body is poorly tolerated by the body. However, other antitumour drugs are also not well tolerated by the body, and like lactate, are not broken down (metabolized) by the body and continue their toxic effect till their elimination from the body, or forever.

In this connection, it can be assumed that the local injection of lactate into the malignant tumour area will allow the suppression of tumour growth, and the gradual flushing out of lactate from tumour and its distribution in the body will not cause significant damage to the body.

CONCLUSION

This review paper was an attempt to analyze fundamentally the existing literature on the topic of the genesis of cancer and point out relatively new theory of oncogenesis on the basis of conclusions that were made. In the framework of this theory, the majority of the known phenomena observed in oncogenesis can be explained. Among the most important foundations of the proposed theory are the role of evolutionary factors, the instability of the genome in malignant cells and the role of chromomeres in these cells. In addition, the work proves new ideas about the mechanisms of cell malignancy, the changes in the transformation process of genetic programs that control this cell, the causes of biochemical and structural changes in the cell as well as the reasons for the considerable variability in the timing of malignant tumours.

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