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Research article

Opinion: Molecular Genetic Aspects of Carcinogenesis at its Different Steps

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Abstract

On initiation stage of carcinogenesis, normal somatic cells after fusion process forms dikaryons, carriers of high carcinogenic potency, and then, after karyogamy - hybrid synkaryon (precancerous cell). Mechanism of malignant transformation of precancerous cell into cancer cell has the molecular and sub-cellular conditions: gene amplifications and chromosomal aberrations. Malignant tumors have clonal origin, and in initial stage consist of genotypically identical cells. Cellular subpopulations are constantly formed in tumors without any obvious regularity, and in any other tumor there can coexist phenotypically and genotypically different cells.

Keywords: Carcinogenesis, Initiation, Promotion, Progression, Invasion, Metastasis, Perforation, Fusion, Karyogamic Theory

1. INTRODUCTION

Among the hypotheses and theories dedicated to the problem of carcinogenesis, karyogamic theory belongs to those rare theories which deals with both etiology and pathogenesis of cancer formation [1]. This theory maybe considered as general (common or integrate) theory of carcinogenesis, which includes the principal aspects of the most popular and acceptable theories and hypotheses for today [2,3]. Based on this theory it was suggested that influence of

diametrically different carcinogens on target cells probably are adequate. After their influence, cells' fusion originates as a result of cytoplasmic membranes perforations [4]. It would be interesting to discuss details of the genetic aspects related with each stage of the carcinogenesis (initiation, promotion and progression).

2. INITIATION

Polypotent cells or other commited cells sensitive to carcinogenic effects and capable of proliferation form firstly dikaryons (hetero- or homokaryons) and than hybrid cells (synkaryons) by means of fusion with another cells of the same organism, in particular, with differentiated and non-differentiated cells of corresponding tissue or with cells capable to migrate (macrophages, lymphocytes, granulocytes of different maturity and so on).

In all probability, during the perforation or modification of the plasma membrane, i.e., after the formation of pores, induced by different carcinogenic agents and factors, the total charge of this organoid changes and cells develop the ability to come closer to each other, which frequently, especially upon coincidence of the perforated parts, will probably be the prerequisite to a fusion process [5].

In the opinion of adherents of the virus-genetic theory of carcinogenesis, it is hard to imagine that influence of cellular surface by carcinogens may alter cells' genome; moreover, that inherited character of malignant transformation supposed exactly the cellular genome alteration. From the position of the karyogamic theory of carcinogenesis, the action of any carcinogen is not associated directly with gene apparatus of cells. Alteration of the cell's genome is induced indirectly.

It is necessary to emphasize that in most cases, hybrid cells probably perish in this stage as a result of lethal fusion of nuclei. On the other hand, after their successful fusion mononuclear synkaryon is formed, which is differ from normal parent cells genotypically and possess on the early stage tetraploid or hypotetraploid sets of chromosomes. Fusion immediately doubles the number of chromosomes, thereby decreasing the chances that the loss of some chromosomes will kill the hybrid cell. In synkaryon, formed on the following stages of development, the segregation, i.e., elimination of definite chromosomes, is possible. More often, in precancerous cells, an assumptive set of chromosomes must be hypotetraploid or hyperdiploid one.

Precancerous (initiated, immortal) cells-synkaryons in phenotypic respect, in most cases, are almost indis-tinguishable from normal cells of these tissue, as they retain morhology similar to the one of the parent cells. Only in rare cases, because of intermediate heredity, precancerous cells may have morphology of the both parent cells simultaneously, i.e., intermediate morphology. These synkaryons differ from normal cells only by their genotype, having tetraploid chromosome set at the initial stage of fusion, and then hypotetraploid, hyperdiploid set of chromosomes and so on. Precancerous cells, can be remained in the organism in latent state for indefinite by long time, probably in some cases for decades.

Taking into consideration the plurality and variety of environmental carcinogenic agents and factors around us, and also the fact that the thepolypotent cells, stem cells, lymphocytes, macrophages and commited cells exist in all tissue of macro organism, one can suppose that precancerous cells can often be formed in many tissue and organs simultaneously. Thus, theoretically, we can expect that in all tissue of one organism can be simultaneously accumulated precancerous cells. For example, there are communications about simultaneosly developed tumors of different localization and histogenesis [6].

Thus, on initiation stage of carcinogenesis, normal somatic cells form dikaryons, carriers of high carcinogenic potency, and giant polykaryocytes.These last cells in most cases, are nonviable cellular formation, i.e., in the genetic respect, they probably are defective peculiar forms, with the lost abilities to enter in S-period of cellular cycle and mitosis. Giant polykaryocytes, in the whole, must be interpreted solely as a reactive process, carried out in all tissues and organs of macro organism at pathologic states. Thus, it is necessary to take into consideration that the appearance in certain tissues and organs of polykaryocytes can signify presence of conditions for cells' hybridization and, consequently, potential possibility of appearance of tumorous dikaryons and then synkaryons.

3. PROMOTION

The mechanism of malignant transformation of the precancerous cell into a tumorous one probably has the molecular and sub-cellular foundations.

For tumor promotion (i.e., formation of tumorous synkaryon) the necessary precondition is active proliferation (hyperplasia) of the corresponding tissue. In the process of promotion, i.e., under the effect of perfect carcinogens, promoters, non-specific influences or some extreme situations (fractures, traumas, and resections) stimulating

carcinogenesis, a precancerous synkaryon can transform into a tumorous synkaryon. Prolonged proliferation of cells caused by various reasons is one of the major conditions, during which the carcinogenic potency of different substances and factors fully manifests itself.

Thus, in the process of promotion, a precancerous synkaryon can be transformed into tumorous one. The mechanism of malignant transformation probably has the molecular (sub-cellular) conditions. Some sites of certain chromosomes seem to have a great significance for the control of the intensity of cell's proliferation and differentiation. In rare cases, as a result of specific chromosome translocation or other chromosome aberrations, which may lead to the amplification of genes, controlling the intensity of proliferation, the so-called "over-expressed gene" can be formed [7]. It is necessary to emphasize that in resemblance with diploid cells, in cells with tetraploid (likely, with hypotetraploid or hyperdiploid and so on) set of chromosomes clearly tend to formation of chromosomes' aberrations. Over-expressed genes may function permanently, coding so-called cancer albumen (or the "growth factor") in great amounts, then suffer anomaly activity of cell, which is characteristic for malignant state. In this case, the precancerous cell acquired the ability of intensive and uncontrolled proliferation. These cells may pass into the stage of promotion, i.e., they transforms into true tumorous synkaryon. This last cell acquire selective advantage over the normal cells.

As known, complete carcinogens and initiators can induce damage on level on genes. Such damages are: gene amplification, protooncogene activation, violations of DNA physiological methylation and so on. Violations can be brought on chromosomal level as well. Such alterations are chromosomes structural aberrations, such as translocations (reciprocal and nonbalanced), deletions, duplications, inversions. Chromosome number alterations (heteroploidy), ultimately make conditions for aneuploidy of a chromosome set, attribute loss or addition of separate chromosomes (or locus of chromosomes), what takes place as a result of their incorrect divergences in mitosis [8,9].

In a process of promotion, i.e., influence of carcinogens, promoters or modifying factors, which stimulate proliferation of somatic cells, precancerous cell, in some rare cases, as a result of chromosomal translocations or of other types of chromosomal aberrations, what, for its part, can lead to genes amplification, can be transformed into tumorous synkaryon.

Thus, structural alterations, i.e., aberrations of chromosomes, usually lead to the loss (deletion) or acquisition of individual sites of chromosomes, i.e., to nonbalanced or reciprocal translocations and duplications. Transferring of part of genetical material from one chromosome to another, ultimately, can lead to the alterations in expression of definite genes. It is necessary to mark that the transfer of genetic material from one chromosome to another occurs not only in translocations, but in other types of chromosomes' aberrations, too. For instance, in duplication of one chromosome, or in different nonhomological chromosomes, analogous sites of chromosomes (in several specimens) are present, having the same function. Duplicated sites in chromosomes frequently form the tandem, i.e., they are located one after another. As to deletion, maybe this type of chromosome aberration in some cases also participate in gene's activation, but, of course, not by amplification of one or another oncogene. In the case of deletion, as it is known, the loss of genetic material is observed, which can lead to the expression of the oncogene, which was controlled (e.g., repressed) by the lost chromosome site.

Thus, in the mechanism of oncogenes' activation, different structural aberrations of chromosomes (translocations, duplications and possibly deletions) can take part. However, the majority of researchers put the main accent on chromosomes' specific translocation, as on reciprocal, as well as especially on nonbalanced translocations.

It is probable, that gene amplification is one of the possible mechanisms of cellular oncogene activation, what can lead to undesirable gene's expression resulting in abnormal proliferative activity of precancerous cells.

The actual existence of the above-mentioned molecular (sub-cellular) mechanism of normal somatic cells' transformation has been confirmed by recent studies, which establish that various carcinogenic factors and influences are the inductors of genes' amplification [10,11]. Theoretically, even a single amplification of corresponding genes by any dose of promoters is a sufficient condition for conversion of normal cells into malignant state.

Tumorous cells formed by means of above mechanism, because of expression or the increase of dose of genes, are distinguished by their ability to more intensive proliferation, what gives selective advantage as compared with the normal cells. After one cellular division, such cell may get over the rails of progression.

Why is the oncogenic diseases comparatively rare? On the one hand, taking into consideration the environment of human external carcinogenic background and plurality of complete carcinogens and also initiators, one can make assumptions about the frequent origin of precancerous cells. On the other hand, at promotion, to transform precancerous cells into tumorous ones, some coincidences on the molecular and sub-cellular levels are necessary

(nonbalancedtreanslocation or other chromosomal aberrations, genes' amplifications). Out of the numerous dikaryons and synkaryons formed after the influence of carcinogenic agents, only a few precancerous cells can acquire the potency of unlimited proliferation. In the overwhelming majority of cases, they seem to die in the phase of transformation into tumorous cells due to lethal mitosis. Specifically, because of the imbalance of karyotypes, they either never reach mitosis or are unable to complete it due to disturbance in spindle organization or chromosomes motion. Therefore, true tumorous synkaryons are probably formed very rarely.

4. PROGRESSION

Any combinations of cancer cell with other differentiated and nondifferentiated normal somatic cells are possible. This is the reason for different histogenesis and heterogeneity (morphologic, cytogenetic, antigenic and, etc.) of tumorous cells. Thus, the population of tumorous cells, as morphologically, as cytogenetically (and on other signs) in spite of clonal origin of tumors, often is highly heterogenous. Cellular subpopulations are constantly formed in tumors without any obvious regularity, and in any other tumor there can coexist phenotypically and genotypically different cells.

In the case of progression, generalization of tumor process, exacerbation, a transition to a more malignant stage take place. The progression stage, as it seems, should be conditioned by two radically different from one another properties of a tumor cells, which is being manifested in the ability to develop invasion process, in the one case, and the metastatic process, in the other case. These two processes, i.e. invasion and metastasis, significantly differ from one another by their development, cellular mechanisms, etc. In particular, in the invasion process, inclusion by tumor cells of the neighbor new normal somatic cells in the fusion process takes place, as a result of which tumor cells of new phenotype and genotype are formed. In contrast to it, in the metastasis process, the development of secondary tumors in a macro organism takes place, as a result of breaking-away of some cells from the initial tumor. In the case of invasion and metastasis,a great importance in seemingly given to a changeable electric charge value. However, if in the case of metastasis the electric charge on the tumor cell's surface counts during almost the whole process, in the case of invasion such charge will count only upon a contact between a tumor cell and its neighbor normal somatic cell, which enables the convergence and further adhesion of these cells.

4.1. Invasion

Separate clones of specific malignant tumors can differ from each other in many abilities, including their metastatic potency, antigen composition, sensitivity to different factors and influences and so on. The origin of clonal divergence may be the consequence of genetic instability of tumorous cells, what unlimitely leads to the tumor progression. The genetic mechanism of tumor progression and tumorous cells heterogeneity is so far vague and possibly depends on complicated interrelation between the macro organism and the tumor.

We can make the assumption that the possible mechanism of morphological, cytogenetical, etc., heterogeneities of cancer cells and tumor invasion consistent in the further involuntary somatic hybridization of these cells. Moreover, it may be possible that in tumorous cells, in resemblance with normal ones, the ability for somatic hybridization is abnormally high.

Thus, it may be supposed that a possible mechanism of invasion process is the hybridization of somatic cells, i.e., the already formed tumorous cells can often be hybridized both with the same cells and with normal cells [12]. After the fusion with other tumorous cells or with normal cellular elements, formation of dikaryons may take place, in which one nucleus can be represented by tumorous cells, and the second, by normal cells (in case of fusion of tumor and normal cells). After synchronous mitosis or mechanical assembly of nuclei in such cells, a hybrid cell-synkaryon can be formed. This cellular type is represented with new genotypic (and in some cases phenotypic, as well) signs.

4.2. Metastasis

Only some cells of the primary cancer are able to metastize (the ability of breaking off from the main focus, migration and attachment to a new place). Once the cancer cell is detached from the primary tumor, it will penetrate blood vessels, retaining viability under the damaging and lethal to it influence, such as blood turbulence and contacts with the immune system cells. Further, by passing the basement membrane, it will go from the blood-vessel

endothelium to the target organ. In order to perform such a complex migration, it is necessary that essential alterations of electric potential on the plasma membrane of the cancer cell take place, which should be associated with the hydrogenous index (pH) changes. The membrane potential of a cancer cell plasmalemma should be connected with the changes of physical and chemical nature occuring in the body, as well as with the metabolic activity of this type of cells proper. In the case of a relatively suppressed metabolism of cancer cells, the enviromental pH increases. In the case of high pH, a cancer cell may develop a high negative charge, which suppresses its adhesion with the tumor bulk and can lead to its detachment and migration in the macro organism. In the event of enhanced metabolism of a cancer cell, the environmental pH is suppressed, as a result of which cancer cells acquire a relatively low negative, neutral or even a positive charge on their surface. Should a metastatic cell change its high negative charge for a relatively low, neutral or even a positive charge, its attachment to a new place and the formation of new cancer cell populations will be quite real. In contrast to metastasis, invasion process should take place only if cancer cells have a low negative, neutral or positive charge.

CONCLUSION

Among the processes in which the normal eukaryotic somatic cells-built programs participate during the body's vital activity, the following should be mentioned: mitosis, differentiation, interphase, phagocytosis, endomitosis, apoptosis, necrobiosis, adhesion, and, certainly fusing. When speaking about biological essence of fusing, its possibility to create polyploidy in somatic cells (like endomitosis) that intensifies resistance of respective organ to negative environmental factors deserves mentioning. Regrettably, this necessary on the face of it for the organism process is associated with the risks of malignant transformation of the fusion-developed binuclear and polyploid cells.

As a resut of karyogamy, i.e., after synchronous mitosis or simple mechanical assembly of nuclei heterokaryons (or homokaryons), mononuclear hybrid precancerous cells develops, with tetraploid set of chromosomes on initial stage of hybridization. Received as a result of somatic hybridization, the hybrid synkaryon is an precancerous cell, which exists in macro organism indefinitely for a long time. On the promotion stage, after the influence of perfect carcinogens or promoters on tissue, where precancerous cells pre-exist, in these cells, the chromosomal aberrations of different types and genes amplifications may arise. From the chromosomal aberrations, the most dangerous in carcinogenic respect are nonbalanced translocations, and also duplications, expressed in "complementation" of chromosomes' identical sites, having the same function. This event usually leads of genes' amplification, in consequence of which expression of genes (oncogenes), responsible for the control under the cellular proliferation, ultimately may originate. At the initiated stage of its formation, precancerous synkaryons evidently possess tetraploid or hypotetraploid set of chromosomes. Further, in the process of tumor progression after the segregation of some chromosomes, they may arise tumorous cells with aneuploid or even hyperdiploid set of chromosomes. After this, tumorous cells with extreme polymorphism of karyotype and new abilities arise.

Notwithstanding the fact that a tumor substrate originates initially from one synkaryon, or despite its clonal character, in most cases, the tumorous cells of highly morphologic and cytogenetic polymorphism originate. Cellular subpopulations are constantly formed in the tumor focus without any obvious regularity and can coexist in the phenotypically and genotypically distinguished cells. Thus, malignant tumors have clonal origin and on initial stage consist of genetically identical cells. In the future, cellular substrate of tumors develops continuously and alters genetic properties. Karyogamic theory explains these facts by spontaneous somatic hybridization between tumorous cells, or tumorous and precancerous cells, or between tumorous and normal cells of tumor substrate.

At first site, the drawback of karyogamic theory is the existence of malignant neoplasms with diploid set of chromosomes on tumorous cells [13]. However, it is necessary to emphasize that diploid set of chromosomes in tumorous cells does not signify absence of process of somatic hybridization in these rare cases. In cancer cells, one part of 46 chromosomes (in case of human) maybe from one initial cell, but the other part of chromosomes may represent the second parent (initial) cell (pseudodiploid clone); for instance, 20+26. Above-mentioned quantity of chromosomes (46), undoubtedly, is one of the most balanced for cancer cells.

It is interesting in this respect, that in some malignant tumors there are marked near-diploid or hyperhaploid chromosome modes. A near-haploid chromosome number of 29 to 30 was found in a melanoma and in case of metastatic melanoma characterized by a hypohaploid chromosome number of 24 [14]. Kovacs and his co-authors (1988) communicated about 70 cases of renal cell carcinomas, which usually showed near-diploid chromosomal modes [15]. In our opinion, these near-haploid and near-diploid chromosomal modes are result of tumorous cells chromosomes' selective segregation during carcinogenesis.

From the view of kariogamic theory of carcinogenesis we are trying to answer one of the most complex questions in oncology: are the chromosomal aberrations the cause or the consequence of the cancerous growth? We hypothesize that during initiation (formation of precancerous cells) chromosomal aberrations (quantitative aberrations) are on the third place after the perforations of the plasma membrane and fusogeny (formation of dikaryons and then synkaryons). During promotion chromosomal aberrations (first of all structural aberrations) are on the first place before the gene amplification. In the case of progression (formation of cancerous cells with a new genotypes and phenotypes) the sequence should be the same as for the initiation (perforations, fusogeny and after that - chromosomal quantitative aberrations). So the role of chromosomal aberrations differs at the different stages of carcinogenesis, but there are no doubts about their causative connections: at the stages of initiation and progression chromosomal aberrations are among the main causative factors (after the plasmatic membrane perforations and fusogeny), while at the stage of promotion, the main causative factor is the structural chromosomal aberrations.

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REFERENCES

[1] Hallion, L. Le probleme du cancer et la biologiegenerale. Press Med Par. 1907; XV :601-603.
[2] Gogichadze, GK., Gogichadze, TG. Karyogamic theory of cancer cell formation from the view of the XXI century.Nova Biomedical Books, New York, 2010.
[3] Gogichadze, GK., Gogichadze, TG. Somatic hybridization, as a primary reason of malignization. Lambert Academic Publisher, Saarbruken, 2013.
[4] Gogichadze, GK., Gogichadze, TG.,Kamkamidze, GK. Presumably common trigger mechanism of action of diametrically different carcinogens on target cells. Cancer and Oncology Research, 2013, 1 (2) :65-68.
[5] Gogichadze, GK., Misabishvili, EV.,Gogichadze, TG. Tumor cells formation by normal somatic cells fusing and cancer prevention prospects. Medical Hypotheses, 2006, 66, 1 :133-136.
[6] Meloni, G., Proia, A., Guerrisi, V. et al. Acute myeloid leukemia and lung cancer occurring in a chronic lymphocytic leukemia patient treated with fludarabine and autologous peripheral blood stem-cell transplantation. Ann. Oncol. 2000, 11 :1493-1495.
[7] Bea, S., Ribas, M., Heranandes, JM. et al. Increased number of chromosomal imbalances and DNA amplification on mantle cell lymphomas. Ann. Oncol. 1999, 10 :101.
[8] Heerema, NA., Nachman, JB., Sather, HN. et al. Hypodiploidy with less than 45 chromosomes confers adverse risk in childhood acute lymphoblastic leukemia: a report from the children's cancer group. Blood. 1999, 94 :4036-4045.
[9] Vanasse, GJ.,Concannon, P., Willeford, DM. Review: regulated genomic instability and neoplasia in the lymphoid lineage. Blood. 1999, 94 :3997-4010.
[10] Sturm, SA., Strauss, PG., Adolph, S. et al. Amplification and rearrangment of C-myc in radiation-induced murine osteosarcomas. Cancer Res. 1990, 50 :4146-4153.
[11] Lonn, U., Lonn, S., Nylen, U. et al. Amplification of oncogenes in mammary carcinoma shown by fine-needle biopsy. Cancer. 1991, 67 :1396-1400.
[12] De Baetselier, P. Neoplastic progression by somatic cell fusion. Influence Tumor Dev. Host. Dodrecht, etc., 1989.
[13] Walker, J., Quirke, P. Biology and genetics of colorectal cancer. Eur. J. Cancer. 2001, 37 : 163s-172s.
[14] Atkin, NB., Baker, MC. A metastatic malignant melanoma with 24 chromosomes. Hum. Genet. 1981, 58 :217-219.
[15] Kovacs, G., Soudah, B., Hoene, E. Binucleated cells in a human renal cell carcinoma with 34 chromosomes. Cancer Genet Cytogenet. 1988, 31 : 211-215.

