Short communication

Assumptions about the invasion and metastatic processes of carcinogenesis

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Abstract

Apparently, invasion should occur only in the case when cancer cells have a low negative, neutral or even a positive charge. On invasion process is developed by involvement of new, intact cells and tissues into carcinogenesis, where a great role should be given to somatic hybridization. At this time, tumor cells of a new type are being formed. Cancer cell can switch on and activated biochemical processes, enhancing thus the metabolism of these cells. As a result, the environmental pH is suppressed, in consequence of which cancer cell acquire a relatively low negative, neutral or even a positive charge of their surface. And vice versa: in the case of a relatively suppressed metabolism of cancer cells, the environmental pH increase. 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. Should a metastatic cell change its high negative charge for a relatively low negative, neutral or even positive charge, its attachment to a new place and the formation of new cancer cells populations will be quite real.

Keywords: human papilloma virus, adolescents, vaccination, kenya

Introduction

Among the theories of carcinogenesis, karyogamic theory belongs to those rare theories which deal with both etiology and pathogenesis of cancer formation. This theory maybe considered as general (integrate) theory of carcinogenesis, which includes the principal aspects of the most popular and acceptable theories for today. Based on this theory it was suggested that influence of diametrically different carcinogens on target cells are adequate. It would be interesting to discuss details of invasion and metastasis processes from the standpoint of karyogamic theory of carcinogenesis.

Progression

Any combinations of cancer cells with other differentiated and nondifferentiated normal somatic cells are possible. This is the reason for different histogenesis and heterogeneity of tumorous cells. Thus, the population of tumorous cells, as morphologically, as cytogenetically (and on other signs) in spite of clonal 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 can coexist there 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 metastatic process the development of secondary tumor focus in macro
organism takes place, as a result of breaking-away of some metastasize cells from the initial tumor focus. 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 inzasion such charge will count only upon a contact between a tumor cell and its neighbor normal somatic cell.

The origin of clonal divergence may be the consequence of genetic instability of tumorous cells, what unlimitedly leads to the tumor progression. 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.

We suppose that the process of invasion is taking place when the tumor tissue’s pH is low. If we ratonate, in the presence of a high negative charge cancer cells should not have the ability to effect somatic hybridization with other cells with such intensity. Apparently, invasion should occur only in the case when cancer cells have a low negative, neutral or even a positive charge. Concurrently, the prerequisite for fusing of cells are perforations of the plasma membranes of both cellular partners. In case the plasma membranes of these cells lack pores (holes), these cells will contact with each other but without fusing. The same result is expected in the case of availability of pores in the plasma membrane of one cellular partner only.

On the other hands, the active cell metabolism has been found to condition the suppression of pH towards the acid medium. In its turn, the acid medium contributes to the formation of pores (holes) in the plasma membranes of cells, this being accompanied with the negative electric charge suppression on the cell surface. This circumstance is contributive to cell-to-cell contacts, further adhesion and fusing. Moreover that the possibility of the formation of dikaryons or symplast-like structures during low pH is a long-established fact. Thus, in the case of low pH it is quite possible that the formation of pores on plasma membranes of both partner cells, adhesion, the formation of dikaryons, then karyogamy and, as a result, the process of invasion can take place. In the case of invasion, further genotypic and phenotypic changes are taking place [1].

Thus, invasion process developed by involvement of new, intact cells and tissues into carcinogenesis, where a great role should be again given to somatic hybridization. At this time, tumor cells of a new type are being formed. As it is well-known, the genotypic and phenotypic instability is the primary manifestation in cancer.

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 be often hybridized both with the same cells and with normal cells [2]. 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.

**Metastasis**

To understand the mechanisms responsible for metastasis is one of the priority goals of cancer research. This process remains one of the most enigmatic aspects of this fatal disease.

Only some cells of the primary cancer are able to metastasize (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 its influences, such as blood turbulence, contacts with the immune system cells and so on. Further, by passing the basement membrane, it will go from the blood-vessel endothelium to the target organ. Thus, in order to initiate the process of metastasis, the cancer cell must get detached from the primary tumor seat and penetrate the basement membrane twice in two different directions – from the tumor seat to blood vessels (capillary) and then from the blood vessels to the target organ’s tissue. In order to perform such a complex migration, it is necessary that essential alterations of electric potential on the plasma membrane of the cancer (metastatic) cell take place, which should be associated with the hydrogenous index (pH) changes. Overall, the process of metastasis can, as it seems, be divided into 6 stages:

1. The growth of a new network of blood vessels, called tumor angiogenesis. Vascularization is a fundamental step in the transition of tumors from the dormant state to the malignant one. To activate the process of vascularization, cancer cells release the angiogenic diffusible factor (angiogenic growth factor), which creates vasculature in the tumor focus.

2. The metastatic cell’s breaking away from the primary cancer focus. It has been established that in the tumor tissue, against the surrounding normal tissue, there is generally low pH [2,3], although it is not excluded that depending on variable metabolism, pH could be somewhat higher. In the case of high pH, the cancer cell can develop a high negative charge, which will, undoubtedly, suppress it sticking (cell-cell interactions, adhesion) to the tumor and its detachment from the seat will be quite real.
The metastasic cell’s entry in the blood vessel (more in capillaries owing to the thin wall), presumably, manages through a special enzyme or pores available in the vascular epithelium.

The metastasic cell’s circulation. Most often, the cancer cells break off and travel in the bloodstream. If these cells travel through the bloodstream, they can get to any part of the body. If the metastatic cells circulate through the lymph system, they may end up in the lymph nodes or spread to other organ. The absolute majority of metastatic cells is destroyed exactly in the period of circulation.

Metastatic cells exit from the blood vessels by means of diapedesis. To breach the basement membrane, metastatic cells use either the pores available in the endothelium of capillaries or release specific enzymes, called metalloproteinases. These enzymes facilitating diapedesis from blood vessels.

The attachment of the metastatic cell to a new place. If the metastize cell continues to retain a high negative charge, its attachment to a new place is excluded. A diametrically different situation will be created in the case if the metastatic cell changes its high negative charge to a relative low, or even the positive one. In such case, its attachment to a new location and the formation of new colonies (or metastases) of cancer cells can be quite possible.

The membranes potential of a cancer cell plasmalemma should be connected with the changes of physical and chemical nature occurring in the macro organism, as well as with the metabolic activity of this type of cells proper. The hydrogenous index (pH) is permanently changing in the body because of cells metabolism. The cancer cell metabolism has been found to differ from the normal cell metabolism. Cancer cells can switch on and activated alternative biochemical processes, enhancing thus the metabolism of these cells. As a result, the environmental pH is suppressed, while metabolic by-products are used for construction of new cancer cells [3,4]. In the case of a relatively suppressed metabolism of cancer cells, the environmental 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 negative-ta-sta-tic cell change its high negative charge for a relatively low negative, neutral or even a po-sitive charge, its attachment to a new place and the formation of new cancer cell populations will be quite real.

Concretely, in what should the mechanism of the negative charge suppression on the cancer cell surface consist? Evidently, it should be associated with the suppression of the concentration of neuraminic acid (sialic acid) that is found on the cell surface thanks to different, often diametrically oppositely causes (pH, virus, radiation, etc.). This acid is in direct association with the value of the negative charge on the plasmalemma surface and vice versa. Hence, in the case of low pH, the neuraminic acid content can be significantly suppressed, changing thus the high negative charge on the cancer cell surface to a relatively lower one, or even to the positive one. It should be observed here that besides pH there are both exogenous and endogenous causes of the charge suppression (virus, toxin, irradiation, carcinogenic hydrocarbons, adsorption of antibodies on the cell surface, increased concentration of albumins and globulins, heparin, high-molecular solutions of gelatin and dextran, etc.).

It appears that as a result of disappearance of the neuraminic acid from the cell surface owing to various reasons (low pH, virus, toxin, etc.), the cancer cell’s plasma membrane tends to form pores, contributing thus to the negative charge reduction and stimulation of the process of adhesion between cancer cell and normal cells in its new place of attachment, which may become a prerequisite for adhesion (or attachment) – the final stage of the process of metastasis [5-9].

References