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Short Communication

Supposition about absence of contact inhibition of cancer cells

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As is known, the superficial charge of most somatic cells is negative. Proceeding from this fact, somatic cells never interact. There is always some type of space (intercellular space) between them. Intercellular contacts are predominantly determined by two main factors: Van der Waals (positive taxis) and electrostatic (negative taxis) forces contributing to the formation of membrane electric potential. Presence of the intercellular space is a structural representation of the balance between these forces (contact inhibition).

A cancer cell has, generally, on its surface a high negative electric charge, which frequently interferes with its approaching and contact, as well as further adhesion with a normal somatic cell (which also has a negative electric charge on its surface).

As early as in the 50s-60s of the 20th century, the malignant cells' feature to lose the ability of contact inhibition was found. Because of this, they do not stop contacting with normal somatic cells (or cancer cells), continue, in some cases, their division (mitosis), and finally even craw over them [1].

In our opinion, the loss of contact inhibition by a cancer cell should be closely associated with the carcinogenesis of stage I – initiation and stage II – progression, more specifically, with the two diametrically different manifestations of progression – the processes of invasion and metastasis. Invasion, the defining feature of malignancy, is the capacity for tumor cells to disrupt the basement membrane and penetrate underlying stroma [2]. Metastasis involves the spread of cancer cells from the primary tumor to surrounding tissues and to distant organs and is the primary cause of cancer morbidity and mortality. In order to complete the metastatic cascade, cancer cells must detach from the primary tumor, intravasate into the circulatory and lymphatic systems, evade immune attack, extravasate at distant capillary beds, and invade and proliferate in distant organs [3].

As is known, upon invasion cancer cell contacts with the neighbour normal or precancerous cells and different cooperation between them take place. A completely different picture is produced in the case of metastasis. Cancer cells are known to have weak adhesion ability in relation to one another (certainly due to high negative charge). Thus, at the stage I of metastasis, cancer cells easily dissociate, detach from the main (primary) tumour focus and may be transported for a long distance by the blood and lymph. As a result, the secondary cancer – metastasis can be formed in the last stage of metastasis. This can happen only if the cancer cell loses the contact inhibition ability, or if a comparatively low negative, neutral and/or even positive charge, rather than the high negative one will be on its plasma surface [4,5] because of which it will be able to adhere to a new focus.

As it seems, a cancer cell is characterized by alternating electric properties, i.e. it has the ability to alter in correlation with different processes and factors (metabolism, proliferation, low pH) the electric charge located on its plasma membrane. Nevertheless, why and how should vary the electric charge on the cancer cells' plasma membranes? What process does precede it? The primary reason should be the variable metabolism of a cancer cell and, as a result, the variable electric charge on the cancer cell surface. In other words, the rate of the electric charge on the plasma membrane of the cancer cell should depend on the intensity of metabolism of these cells. The higher are the metabolic processes taking place in cancer cells, the higher should be the proliferative activity of these cells. Hence, owing

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to the accumulation of metabolites in the cell environment, develops a comparatively low pH, which is prerequisite for forming on the cancer cell surface a low negative, neutral, and/or even positive charge. And this will facilitate the attachment of the cancer cell to the secondary, metastatic focus. Here it should be said that the slightest change in pH (even by a decimal measure!) can lead to significant changes in somatic cells' functional state.

Thus, in order to find out the interconnection of the contact inhibition loss by a cancer cell and the carcinogenesis progression stage (invasion, metastasis), the following 4 processes and factors – cancer cell proliferation, metabolism in the cancer cell, environmental pH and the electric charge on the plasma surface of the cancer cell – should be taken into account:

Metabolic pathways may be controlled by the same signals that influence on cell proliferation [6]. In a cancer cell, metabolic networks are highly adaptable. Cancer cells are able to reprogram their metabolic pathways to enable energy production under conditions that are disabling to most normal cells. An extensive metabolic reconfiguration of cancer cells allow them to sustain pathological growth by providing anabolic intermediates for biosynthesis. The higher is the metabolism in the cancer cell, the higher should be its proliferative activity. Or metabolism and proliferation in this specific case are directly correlated.

The higher is metabolism taking place in the cancer cell, the lower is pH, and *vice versa*: the lower is the cancer cell metabolism, the higher is pH. In other words, metabolism and pH are in a reverse correlation.

As regards pH and electric charge, they are in complex correlation to one another. During high pH, a comparatively low negative, neutral and/or even positive electric charge is generated, because of which the cancer cell may lose the contact inhibition ability.

As is known, one of the primary postulates of the karyogamic theory of carcinogenesis consists in the fusion of two normal somatic cells, the prerequisite of which are perforations induced in their plasma membranes by different agents and factors . Presumably, during the massive perforation of plasmalemma induced by different carcingenic and non-carcinogenic agents and factors, the total negative electric charge of this organoid decreases and the cells acquire the capacity of closely approaching to each other.

As has been found, low pH produces perforations – pores in the plasma membranes of somatic cells [7]. Fusion pore expansion constituting the late stage of fusion process leads to membrane rearrangements, whose scales largely exceed those of the fusion protein complexes and vary between tens of nanometers for the vesicle fusion and tens of microns for cell-cell fusion. Such large scale membrane restructuring must be driven by global factors, persisting within large membrane areas or the entire membranes. The most natural candidate for playing a role of such a large-scale fusion factor is the lateral tension [8]. Hence, together with other agents and factors (e.g.,viruses, radiation, toxins, etc.), low pH should be considered as a fusogenic factor. Thus, as a result of perforations induced by low pH in the plasma membranes, reduction of high negative charge to a relatively low negative, neutral or even positive charge can take place. As a result, somatic cells acquire the ability first of adhesion, while in the case of coincidence of the perforated sections of the plasma membranes, that of fusogeny (with formation of dikaryons with high oncogenic potential), and then the ability of somatic hybridization (karyogamy) process [9,10].

What can happen in case a cancer cell loses the contact inhibition ability? The following 2 possibilities should be considered:

In case no perforations (pores) are produced in the plasma membranes of cancer cells and in their neighbour normal somatic cells, and, in parallel, the cancer cells' high negative charge is reduced, not only the contact with, but also their crawl over normal cells will take place.

A different situation can take place upon development of perforations in the plasma membranes of cancer and normal somatic cells, due to low pH, for example. Especially if the relatively high fusogenic activity of cancer cells as compared with normal cell is taken into account (the cause of this should be the established fact that the outer surface of cancer cells is leaky). In case perforations are induced by low pH (as well as by other causes), reduction of the relatively high negative charges of the plasma membranes of cancer and normal cells will occur. As a result, somatic cells will acquire the ability approaching each other and of adhesion, while upon coincidence of the perforated sections of the plasma membranes – that of somatic hybridization (first fusogeny, then karyogamy). As a result, cancer cells with new pheno- and genotypical properties can arise. In this way, cancer cells acquire the property of invading other healthy tissues of the body.

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