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Opinion Induction of Diametrically OppositeCytopathogenic Effects and Clinical Manifestations By Some Viruses

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Opinion

As known, viruses unlike bacteria, are so called "unequipped" pathogens. They don't have exo- endotoxins and other pathogenic factors. So, how do this "primitive" pathogens manage to have such variable cytopathogenic effects and pathologies (infections, teratogenies, malignant tumors)?

It had hardly be said that virus cytopathology has been disregarded in the scientific literature. Not only scientific articles but also special monographs have been dedicated to the issue published long ago [1-3].

The viral penetration and budding stages have particularly attracted our attention, since it is obvious that during of these processes the irreversible and reversible structural changes of the plamalemma are being observed. This circumstance in our opinion can acquire a decisive importance in the possible development of some different, often diametrically opposite cytopathogenic effects and pathologies [4].

Are so wide range of pathologies induced thereby (infections, teratogenic effects, tumor growth) dependent on the specificity of the virus penetration to and withdrawal from the target cells? As it is known, the penetration to the target cell or budding of some viruses (retroviruses, toga viruses, paramyxo viruses, orthomyxovuses, arena viruses, poxviruses) results in the plasmalemma disintegration, triggering in the end perforations of different volume and amount in this organoid. In other words, some viruses trigger massive perforations of the plasma membranes both "from without" (by penetration) as well as "from within" (by budding), during which the cytopathogenic effects of all types with completely different clinical manifestations are expected. At the same time, there are viruses (e.g., some simple viruses) that trigger perforations of the target cells plasma membranes only in the event of penetration.

The absolute majority of complex viruses leave the cell from the plasma membrane by the so-called budding. An exception are some complex viruses that are being budded from the karyolemma (herpes viruses) and from structures of the endoplasmic reticulum (flavi viruses and corona viruses), which in the case of massive release from the cell, may become a direct cause of disintegration of the target cell plasma membrane too.

As it seems, the intensity of virus infections and virulent properties of the virus itself acquire a decisive importance in the development of all types of pathologies (e.g., infections, tumors, etc.), to be followed by the formation of pores of different volume and amount in the process of the target cells plasma membranes penetrations or budding process.

Here should be mentioned the fact that the plasma membrane perforations can also be induced by the virus-associated immune cytolysis. For example, the humoral immune cytolysis has been described for the cells infected with the rubella, herpes simplex, lymphocytic choriomeningitis, tick-borne encephalitis viruses, ortho and paramyxoviruses, etc.

So, in the interrelation between viruses and target-cells we should take in account 3 different perspectives:

1. In the case of multiple penetration or budding, during formation of relatively large-size pores (approximately 8-10 to 100nm), rapid repair of the plasma membrane by the cell becomes impossible and the cell undergoes irreversible changes – destruction (cytolysis). Such an action, as it seem, should be characteristic of the highly virulent strain of some infectious viruses. In other words, viruses may cause infectious (and teratogenic) pro¬cesses:(a) by means of the sequential penetration and budding processes in the event of massive perforation of the plasma membrane (e.g., highly virulent strains

of influenza virus); (b) by means of massive budding processes (e.g., para¬myxoviruses, togaviruses, retroviruses) and (c) by means of going out from target cell by "explosion" (simple viruses, e.g., reoviruses, adenoviruses, etc.), being, accompanied with cell lysis. The clinical manifestation of such cytopathogenic effects can be infectious or teratogenic processes (in the case o damage of the stem cells of any organ) or both of them simultaneously [1-4].

2. In some cases, in the event of formation of pores with smaller volume and amount, together with cytodestruction, viruses induce the formation of nonviable polykaryocytes (in the case of reversible changes of the plasmalemma), which may induce infectious processes (e.g. immunodeficiency of different egree), or teratogenic effects (in the case of damage of the stem cells of any organ). The majority of multinuclear cells (polyka ryocytes, symplasts) probably do not proliferate. They are nonviable, nonfunctional for mations and generally they break down and perish soon after. In carcinogenesis these cells probably do not participate directly but their presence in conforming tissues indicate to the probability of creation of specific conditions for somatic cells' hybridization. Thus, actually all viruses favoring cell's plasma membranes perforation are considered as the possible causes of the formation of malignant tumors.

Thus, the viruses that induce th e for mation of polykaryocytes (or symplasts)-paramyxoviruses, orthomyxoviruses, herpes¬viruses, retroviruses, adenoviruses, poxvirus¬ses, rhabdoviruses, hepadnaviruses, and many others [5-7] can be considered as suspected carcinogens (for they can, in parallel with the formation of polykaryocytes, form dika¬ryons of a high oncogenic potential). Generally, the cell-cell fusion mechanism of plasma membranes underlies the formation of polyka ryocytes. As it seems, the polykaryocytes-forming virus that undoubtedly contains the plas¬ma-membrane enzyme (or enzymes) cause local damages to lipids of this organoid. The clinical manifestation of the formation of polykaryocytes in the macro organism's¬ tissues can be an infectious process, or tera¬togeny.

3. In the case of the formation of pores of more lesser size or amount by the low-virulent viruses, when reversible changes of the plasma membranes are present, the total charge of these organoids changes and the cells develop the ability to come closer to each other (adhesion), which frequently, especially upon coincidence of the perforated parts will probably be the prerequisite to fusion process. Thus, at this stage, together with multi¬nuclear cellular structures, the binuclear cells – the carriers of high carcinogenic potency, are formed [8-10]. As a result of karyogamy, i.e. after synchronous mitosis or simple mechanical assembly of heterokaryons (or homokaryons) nuclei, mononuclear hybrid precancerous cells develop with a tetraploid set of chromosomes in the initial stage of hybrid¬dization. Produced as a result of somatic hybridization, the hybrid synkaryon is the precancerous (initiate, immortal) cell, which exist in a macro organism indefinitely for a long time. From the formation of precancerous cell (synkaryon of stage I) to the manifestation of tumor process, or the formation of proliferated timorous cell (synkaryon of stage II), decades may pass. At the stage of promotion, after the impact of complete (full) carcinogens or promoters on the tissue, where precancerous synkaryons pre-exist, the chromosomal aberrations of all types and genes amplifications may originate in these cells. Out of the chromosomal aberrations, the most dangerous in carcinogenic respect are nonbalanced translocations, also duplications, expressed "complementation" of chromosomes' identical sites, having the same function. This event usually leads to genes' amplification, in the consequence of which the expression of genes (oncogenes) responsible or control under the cellular proliferation may ultimately originates. After the above-mentioned conversion on sub-cellular and molecular levels, there may originate a true tumorous synkaryon the malignant cell with the ability of uncontrolled prolifera¬tion. The latter represents a clone, from which formation of malignant tumors substrate at an early stage of carcinogenesis initiates. Such an action can be characteristic of low-virulent infectious viruses (e.g., influenza virus, some paramyxoviruses, retroviruses, etc.). Out of the numerous heterokaryons (or homokaryons) and hybrid cells (synkaryons) formed after the influence of viruses (and other carcinogenic agents), only a few precancerous cells can acquire the potency of unlimited proliferation [11,12]. In the over-whelming majority of cases, precancerous cells seem to die in the phase of transformation into tumorous cells due to lethal mitosis. Specifically, because of the inbalance (instability) of karyotypes, they either never reach mitosis or are unable to complete it die to disturbance in the spindle organization or chromosomes motion. Therefore, true tumorous synkaryons are probably formed very rarely; their incidence being less than one in 10^6 [13].

Thus, in respect of oncology, dangerous are the low-virulent viruses which (1) penetrate the target cell through membranes, by perforations; (2) are released by budding; and/or (3) lead to cellular-immune or humoral-immune cytolysis.

Of special interest are the diametrically opposite cytopathogenic effects induced by the same virus and the resultant wide range of pathologies [14]. It possible that the same virus could cause both an infectious process and tumor growth, etc.? Or can we suppose that the diametricall opposite cytopathogenic and clinical effects are characteristic of only those viruses, which in the processes of penetration or budding (or during the both processes simultaneosly) cause reversible or irreversible perforations of the plasma membrane of the target cell? Such viruses include: herperviruses (infectious mononucleosis and Burkiit's lymphoma), rubella (infectious process and teratogeny), adenoviruses some serovars (infectious process and experimental cancer), etc. Especially as, according to various scientific data [15-17], some infectious viruses of low virulence or low cytopathogenic action should

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possess fusogenic properties, or the carcinogenic potential. Such are vesicular stomatitis (Rhabdoviridae), parotitis and measles viruses (Paramyxoviridae), some herpesviruses, rubella virus (Togaviridae) and other viruses.

Thus, the infectious and carcinogenic processes, in spite of a principal differences bet¬ween them (for example, the target cells destruction in one case and cytoproliferation, in the other), in certain cases can be induced by the same virus. The seemingly typical onco¬viruses, such as Rous sarcoma and polyoma viruses, can, in some cases, cause various non-tumor pathologies (inflammatory processes, hemorrhages, atrophy of internal organs, etc.), while infectious vi¬ru¬ses may, under certain conditions, acquire the oncogenic potential. Therefore, the same vi¬rus in the case of different virulence and dosage can produce two or even three types of diamet¬rically opposite cytopathogenic and clinical effects.

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