Opinion: Presumable Reason of Interrelationship between Autoimmune Hemolytic Anemia and Cancer Arising

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Abstract: The mechanism of malignant transformation in autoimmune hemolytic anemia can be based on the inclusion of immunocompetent cells in different cellular cooperations. Antibodies and T-cytotoxic cells can induce perforations of different degree on somatic cells plasma membranes. Total negative charge of plasma membranes decrease, and the cells acquire the capability of closely approaching, which frequently, especially upon coincidence of the perforated parts, may serve as a prerequisite to fusion process and formation of cancerous cell.

Keywords: Hemolytic anemia, immunocompetent cells, organic and inorganic hemolytic toxins.

There are hemolytic anemias of different origin. They may be induced by means of some exogenic hemolytic factors: by different organic and inorganic hemolytic toxins (phosphorus, phenylhydrazin, saponins, arsenicum, lead) and biotoxins (snake venom, mushroom poisons, mycotoxins, etc.), some medical preparations, radiations, some infectious agents and heavy burns. Besides, in some cases, hemolytic anemias are induced by antibodies and immunocompetent cells against own tissues (autoimmune hemolytic anemia). Reason of immunization of autoimmune hemolytic anemias may be infectioos diseases (grippe, malaria, acute anaerobic or streptococcal sepsis, pneumonias etc.) and some other physical and chemical factors and influences.

A strong relationship exists between autoimmunity and B-cell oncogenesis. According to clinical studies malignant tumors in autoimmune hemolytic anemias appear in 45-47%. Observation of a large body of literature, permit to suggest that quite frequently tumor cells in autoimmune hemolytic anemias have lymphoid and macrophageal nature. The analysis of 234 patients with autoimmune hemolytic anemias showed chronic lympholeukemias, malignant lymphomas, multiple myelomas, alimentary tract cancers and so on [1]. The analysis of 168 patients with hemolytic anemias showed approximately similar results [2]. The incidence of tumors of this localization and histogenesis increases significantly in other autoimmune diseases as systemic lupus erythematosus, rhematoid arthritis, etc. [3-5].

According to the scientific opinion, some toxins, even different infectious viruses (for instance, viruses of grippe, rubella and HIV) and carcinogenic agents may induce both fusion process and cytolytic (destructive) effects in somatic cells [6,7]. For instance, the toxin of *Aspergillus flavus* – aflatoxin, except the heavy toxic action, induces malignant tumors (hepatomas) of the liver. Such different effects of these agents on somatic cells possibly depend on the size of plasma membranes' pores induced by them. In the case of large pores, irreversible changes and cytolysis take place. For instance, high doses of carcinogenic agents lead to partial increasing of quantity of giant polynuclear cells, but further increase of this dose induces massive cellular lysis. In low doses of carcinogenic agents, dikaryons (cells, with comparatively high oncogenic potency) are observed most frequently. Presumably, during the perforation of cellular membranes induced by different carcinogenic and non-carcinogenic agents (in this concrete case, by immunocompetent cells and antibodies), the total negative charge of plasma membranes decrease, and the cells acquire the capability of closer approach (adhesion), which frequently, especially upon coincidence of the perforated parts, may serve as a prerequisite to fusion process.

It is possible that during destruction of erythrocytes (or immature cells of this line) by some agents (carcinogens, some toxins, infectious viruses, etc.), in leucocytes damages of plasma membranes and pores of definite size, which may promote process of fusion of somatic cells, may be formed. Larger perforations induce considerable destruction of cell membranes and following cytolysis together with the perishing of these cells [8].

Thus, in hemolytic anemias of different genesis side by side with hemolysis, process of somatic cells fusion

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may take place. For example, there are some assumptions about the association of *Vipera lebetina* bites with the development of cancer of different localization and histogenesis. For instance, after a bite of the venom with hemolytic action (*Vipera lebetina, Vipera Russellii*, etc.) together with massive destruction of erythrocytes (hemolysis), there may be induced a fusion process of other cellular types with more rigid plasma membranes (for instance, leucocytes of different maturity, and probably of cells of other type), with possible development of precancerous, and then true cancerous cell. Approximately similar action one may expect from fungus toxins (*Aspergillus flavus, Penicillium islandicum, Aspergillus ochraceus*, *etc*.).

In our opinion, the mechanism of malignant transformation in autoimmune reactions can be based on the inclusion of immunocompetent cells in different cellular cooperations, which is their normal physiological property.

As it is shown, in case of autoimmune hemolytic anemia or allotransplantations, the macro organism reacts to the modificated (foreign) cells by development of humoral and cellular immune responses (immune cytolysis). In the development of cytolysis the most important roles are played by specific antibodies and T-killer (cytotoxic) cells (immune effectors). Antibody molecules have 2 main functions: they bind to the immunogenic antigens and after interaction with these antigens, they initiate involvement of different cells and molecules. The constant region (C region) of the antibodies defines the type of the response after the antibody-antigen interaction, whether this is complement-mediated lysis, cellular cytotoxicity, enhanced phagocytosis, etc. The cell-immune cytolysis is carried out directly by the killers (T-cytotoxic cells). The cytotoxic effect of these cells is realized in the target cells plasmalemma by special proteins – perforins which lead to the formation in this organoid of perforations (pores). The killers perform their functions either from a distance or when in contact with the target cell. These cells generate substances of cytotoxic and cytolytic action, causing cell necrosis with disintegration of its plasmalemma or induction of apoptosis. Perforins (together with granzymes and granulolyzins) are localized in killer cells (macrophages, T-lymphocytes, NK-cells) granules. In the presence of calcium, perforines interact with the plasmatic membrane of the target cells and after the polymerization they are forming the transmembrane channels (pores) in them. In the case of great number or size, these pores induce the cells destruction or other cytopathogenic effects. So both antibodies and cytotoxic cells can induce damages (perforations) of different degree on somatic cells plasma membranes, which can represent the precancerous and later the true cancerous cells formation [9,10].

Thus, the target cell killing is carried out in several stages: 1) killer-target-cell contact; 2) killer activation; 3) exocytosis of toxic substances by the killer; and 4) toxic effect on the target cell. Thus, pore-forming enzyme, antibodies, peptids, etc. cause plasma membrane damage in target cells, with consequences as diverse as proliferation or cell destruction.

Supposing that leucocytes (in this concrete case, lymphocytes and macrophages) are phenotypially dominant cells, their fusion with each other and with other somatic cells may lead to tumor formation of lymphoid and macrophagal nature. Carcinogenic agents and even infectious viruses and bacterial membranotoxins may induce both fusion and hemolytic effects in somatic cells simultaneously. In autoimmune hemolytic anemias process of somatic cells fusion with further formation of tumor cells may take place, side by side with hemolysis.

Thus, cell fusion may in some cases of autoimmune process produce cells with tumor properties. Carcinogenic agents or some other reasons may create the autoimmunization background in a macro organism, which may lead to multiple intercellular contacts between immunocompetent cells and cells with aberrant antigens. In case of cells fusion, initiation of malignant neoplasms of lymphoid or macrophagal histogenesis is expected to take place.

Consequently, the fusion of immunocompetent cells with other cells may be regarded as a possible cellular mechanism of malignization in hemolytic anemias of different origin. And still, the formation of hybrid cells *in vivo*, may be considered as a physiological phenomenon.

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