

## Allotransplantation and its Association with Rising Incidence of Cancers

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### Abstract

In some cases of allotransplantation, simultaneous development of malignant tumors of different histogenesis may be observed. We propose to consider malignant tumor formation during allotransplantations in terms of karyogamic theory of carcinogenesis. Experience in transplantology tentatively testify that even in cases of maximal antigen compatibility of donors and recipients, immune conflict is unavoidable. As we believe, in immunological conflict between recipient and donor cells, the process of cells' destruction in some cases may be accompanied by damages of plasma membranes and somatic hybridization between immunocompetent cells of the recipient and any cell of transplanted donor's tissue, which may lead to the emergence of a cancer cell. Antibodies and cytotoxic cells can induce damages (perforations) of different degree on somatic cells plasma membranes, which can represent firstly the precancerous and later the true cancerous cells formation.

**Keywords:** Allotransplantations; Cancer; Plasmatic membrane; Perforation

### Opinion Article

Some clinics dealing with problems of transplantology report that recipients with transplanted internal organs (kidneys, skin, bone marrow, etc.) show a significant rise in the incidence of malignant tumor of certain localization and histogenesis [1-6], especially of non-Hodgkin's lymphomas and monoblastic sarcomas. For instance, in renal transplanted recipients was detected 40 to 100 times higher rates of non-Hodgkin's lymphoma and also increased rates of Kaposi's sarcoma. Whereas usually malignant neoplasms of this histogenesis are just a small share of all tumors, during transplantation of internal organs, they are one of the main types of neoplasms. Reported metastatic prostatic carcinoma in a recipient following heart transplantation.

Transplantation of bone marrow is the most complicated type of allotransplantations, because immune conflict develops in two direction: from host to transplanted bone marrow and from transplanted bone marrow to host ("graft-versus-host reaction"). At the same time, many investigators reported that whole blood and hematopoietic stem cell transplantation was associated with a higher risk of malignant process initiation and relapse [7].

Malignancy has become one of the three major causes of death after allotransplantations. Death from cardiovascular disease and infection are both decreasing in frequency from a combination of prophylaxis, interventional therapy and so on.

Different opinions were given regarding the mechanism of tumor development in these cases: 1. Direct carcinogenic influence of immunosuppressors. 2. Activation of endogenous viruses and action of exogenous viruses. 3. Permanent reaction of sensitized donor's lymphocytes against recipient's antigens and so on.

Until recently, the theory of immunological surveillance of F. Burnet [8] seemed to be the most justified one. However, based on a number

of investigation, it may be supposed that immune deficiency is not the necessary condition for the development of malignant tumors and that immune deficiency is the consequence rather than the reason for malignant processes. Old [9] made the same conclusion on the basis of careful analysis of his own and literature data. At the same time, some aspects of experimental biology and clinical medicine could not be explained in terms of immunological surveillance: for instance, why in chronic "graft-versus-host reaction" (also at transplantation of other internal organs) there developed only lymphoid and macrophagal malignant tumors?

Some clinicians are so confident of oncogenic potential of immunosuppression, that they keep immunosuppressive therapy (in the case of allotransplantations) to the minimum level, to avoid development of tumor growth [10]. To our opinion before immunosuppressive therapy in recipient is already established precondition for formation of cancer cell. In the case of varying degree of immune conflict, cytotoxic T-lymphocytes and antibodies lead to formation of different size and volume perforations on the plasma membranes of target cells. By karyogamic theory of carcinogenesis [11], this process may appear as initial step for formation at first of precancerous and later of true cancer cell. Furthermore, as cancer cell lacks of foreign for macro organism antigens and also taking into consideration that occurrence of the cancerous formations in the recipients was almost of the same frequency as for the cases of different immunodepressants (e.g. azathioprine, prednisolone, ionizing and other types of radiation, cyclosporine A, sirolimus, and also the antilymphocytic medicines), we should summarize that immunosuppression should not be considered as direct reason of cancer cell formation.

Concretely, what is the mechanism of tumor conversion on allotransplantation? For the first time, we propose to consider malignant tumor formation during transplantation of allogenic internal organs in terms of karyogamic theory of carcinogenesis [11]. In our opinion, tumorous cells represent the hybrid, the so-called tumorous synkaryon, emerging as a result of the fusion of two normal somatic cells. Stem cells, fibroblasts, macrophages, lymphoid cells,

undifferentiated cells of various tissues and others show an increased capability to create viable hybrids. During the perforation of cellular membranes induced by some carcinogenic and noncarcinogenic substances and influences, the total charge of plasma membranes changes, and the cells acquire the capability of closely approaching (adhesion), which frequently, especially upon coincidence of the perforated parts, may serve as a prerequisite to fusion process. In result of this, may form dikaryons – heterokaryons (cells with nuclei of different type of cells) or homokaryons (cells with homogenous nuclei) in the process of fusion with one another or with other cells, and then, in case of synchronous mitosis or mechanical reunification of nuclei, they may form sinkaryons (mononuclear hybrid cells), with tetraploid or hypotetraploid sets of chromosomes on initial stage of hybridization. The forming hybrid sinkaryon (so-called sinkaryon of stage I) is an initiated, i.e., precancerous cell may exist in the corresponding tissue for a long time, sometimes even several decades. On the promotion stage, after the influence of perfect (full) carcinogens or promoters on tissue, where precancerous sinkaryons preexist, 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. This event usually leads to genes' amplification. After above-marked conversion on sub-cellular and molecular levels, there may arise true tumorous sinkaryon (sinkaryon of stage II), malignant cell with the ability of uncontrolled proliferation [12].

Thus, the common mechanism of action of diametrically different carcinogens (and noncarcinogens) on target cells is the destruction of the plasmatic membrane. After influence of different carcinogens, cells' fusion originates as a result of plasma membranes perforations, what induces alteration of summary superficial charge of cells' surface. Target cells acquire the ability to approach each other, what in many cases may be a premise for fusion process [12].

Experience in transplantology tentatively testify that even in cases of maximal antigen compatibility of donors and recipients, immune conflict is unavoidable. As we believe, in immunological conflict between recipient and donor cells, which is inevitable even under careful selection, the process of cells' destruction in some cases may be accompanied by damages of plasma membranes and somatic hybridization between immunocompetent cells of the recipient and any cellof transplanted donor's tissue (graft), which may lead to the emergence of a tumorous cell.

As it is shown, the recipients reacts to the allotransplantant by development of humoral and cellular immune responses (immune cytotoxicity). In the development of transplantation immunity the most important roles are played by specific antibodies and T-killer cells (immune effectors). 1. Antibody molecules have 2 main functions: they bind to the immunogenic antigens (in this case they are represented by superficial antigens of the allotransplantant cells) and after interaction with the antigen initiates 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. 2. Transplantational cellular immune response is conducted by T-cytotoxic cells: after the sensitization of the recipient by the donor antigens the killer cells are migrating to the transplant tissue and are having inducing the cytotoxic effect. Killers perform their functions either from a distance or when in contact with the target cell. The cytotoxic effect of killers is realized in the target cell

plasma membrane by special proteins – perforins, granzymes, etc., which lead to the formation in this organoid of perforations (pores). Perforins are localized in killer cells (macrophages, T-lymphocytes, NK-cells) granules. In the presence of calcium, perforins interact with the plasmatic membrane of the target cells and after the polymerization they are forming the transmembrane channels (pores). So both antibodies and cytotoxic cells can induce damages (perforations) of different degree on somatic cells plasma membranes, which can represent firstly the precancerous and later the true cancerous cells formation.

Besides, since lymphoid tissue cells as well as macrophages are the morphological substrate ensuring the formation of the immune response to antigenic stimulation, cells of this type may be one of the essential objects in fusion during organ allotransplantation. Moreover, as the process of contact and penetration of lymphocytes to other cells in immunological conflict (“peripolexis” and “emperipolexis”, respectively), as well as facts of fusion of macrophages with other cells are well known [13]. Thus, in the fusion process, the highest activity may be shown by recipient's macrophages and T-lymphocytes, which are effector cells against tissue incompatibility antigens. On the basis of the above and taking into consideration the fact that lymphocytes and macrophages are dominant cells also with respect to phenotypic properties, in the most cases of tumors, malignant cells, which develop during allogenic organ transplantations, may have lymphoid (T- or B-cell), macrophagal or the so-called “intermediate” morphology.

Coming from above mentioned, in transplantations of different allogenic internal organs, bone marrow, and even transfusion of blood and its components (e.g. leukocytes), and hematopoietic stem cells, physicians should take into consideration the likely probability of serious complications due to the emergence of tumorous cells in non-oncological recipients.

## Conclusion

T-cytotoxic cells and antibodies can induce perforations of different size and quantities on somatic cells surface, which can formed the precancerous and later the cancer cells arising.

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