



Review

Tumor Escape from Immune Surveillance

RÉGIS T. COSTELLO^{1, 2}, JEAN ALBERT GASTAUT² and DANIEL OLIVE^{1*}

¹ Laboratory of Tumor Immunology, ² Department of Hematology, Institute Paoli-Calmettes, 232 bd Sainte Marguerite, 13009 Marseille, France, ³ Unit INSERM U119, 27 bd Leï Roure, 13009 Marseille, France

Abstract. The bases for an efficient anti-tumor immune response begin to be better defined. Nonetheless, neoplastic cells develop various strategies to escape immune surveillance, which are discussed here in order to better design the therapeutic possibilities of immune manipulation. The absence of specific tumor antigen as well as the weak expression of major histocompatibility complex (MHC) molecules hinder the recognition of the neoplastic cells by T lymphocytes. The defect of expression by the tumor of the ligands for the T cell activation costimulatory molecules is particularly harmful for the immune response since it induces tolerance. Finally, tumor cells can inactivate effector T lymphocytes through the secretion of inhibitory cytokines, induction of apoptosis or functional inactivation. The multiplicity of the means to oppose an effective anti-tumor response challenges the adaptative mechanisms of the immune system. For example, the natural killer cells target tumor cells not expressing MHC class I molecules. Numerous possibilities of tumor immunogenicity restoration have been demonstrated at least *in vitro*, such as stimulation of the cancerous cells by CD40 or cytokine treatment, which could lead to several promising therapeutical approaches.

Key words: cancer; immunodeficiency; immunotherapy; lymphocyte.

The immune system is a complex and highly regulated defense mechanism which preserves the integrity of the organism by the elimination of all elements considered as “non-self” or “modified self”. The development of cancer constitutes a potentially lethal aggression to the host. Does the immune system participate efficiently to tumor elimination? Clinical data answer at least partly to this question, via analyzes of immunocompromised patient populations and of the immunotherapy approaches already used against cancer.

A highly increased frequency of cancers is observed during the course of congenital immunodeficiency syn-

dromes such as the X-linked immunodeficiency syndrome^{1, 15, 30, 41} or the common variable hypogammaglobulinemia¹⁴. Another example of immunodeficiency corresponds to organ transplantation which requires a strong immunosuppression because of discrepancy between donor and receiver MHC. Therapeutic immunosuppression relies on the utilisation of drugs such as cyclosporin and of corticosteroids, which are powerful inhibitors of T lymphocyte functions. Lymphoma incidence ranges from 1% in renal transplantation to 8% in pulmonary transplantation, and correlates with the intensity of the immunosuppression⁵². In this setting,

* To whom all correspondence should be addressed.

Abbreviations used: MHC – major histocompatibility complex, HIV – human immunodeficiency virus, CML – chronic myeloid leukemia, AML – acute myeloid leukemia, GVH – graft versus host, GVL – graft versus leukemia, APCs – antigen presenting cells, TcR – T cell receptor, IL-2 – interleukin 2, CLL – chronic lymphocytic leukemia, IFN – interferon, NK – natural killer, TNFR – tumor necrosis factor receptor, FL – follicular lymphoma.

the best first line treatment is the reduction of the immunosuppression which usually results in the total disappearance or regression of the lesions. More recently, the HIV epidemic is responsible for an increase in the frequency of many cancers, more particularly systemic or cerebral lymphoma, Kaposi's sarcoma and cervical cancer of the uterus. These data show that immunodeficiency, either congenital, induced by viral infection or related to therapy, favour the development of cancer, especially of lymphoma.

In addition to these data, allogeneic bone marrow or peripheral stem cell transplantation support the existence of an anti-tumor response at least in the case of the malignant hemopathies, such as chronic (CML) and acute (AML) myeloid leukemia. Indeed, donor T lymphocytes recognise the recipient organism as "non-self", a phenomenon called "graft-versus-host" (GVH) reaction. In order to decrease this potentially lethal reaction, attempts of T lymphocyte graft depletion¹⁶ or functional inactivation by anti-IL-2 receptor antibodies have been performed⁵. This graft depletion resulted in reduced incidence and severity of GVH, but also in a very important increase in leukemic relapses. This suggests the existence of graft-versus-leukemia (GVL) reaction mediated by the T lymphocytes. This hypothesis is further supported by the efficiency of the donor T lymphocyte infusion in the treatment of AML or CML relapses^{28, 56, 57}.

Once demonstrated the role of immune system in the antitumor response, and before considering the different mechanisms of tumor escape, we will remind the mechanisms leading to the specific recognition of an antigen by T lymphocytes. First, the antigen (Ag) is degraded in peptides which reach the antigen presenting cell (APC) surface presented by the MHC class I (endogenous peptides) or class II (exogenous peptides) molecules. When a T lymphocyte meets an APC, multiple links between the two cells are created through adhesion/costimulation molecules, which transmit an activation signal to the T cell. Then, the Ag/MHC molecule complex is presented to the specific receptor CD3/TcR. If the Ag presented to the T lymphocyte corresponds to its antigenic specificity, an activation signal is transmitted via the CD3/TcR. The lymphocyte receives therefore two signals, one by the adhesion/costimulation molecules and the other by the Ag receptor, leading to its proliferation, the secretion of the numerous cytokines necessary for the amplification of the immune response – interleukin-2 (IL-2) in particular – and/or to cytotoxic properties. At each step of the immune response, dysfunctions can favor tumor escape.

Absence of Specific Antigen

Various tumor Ags with different levels of specificity have been described. Many neoplasms have chromosomal anomalies leading to the generation of fusion genes potentially transcribed as proteins. One example is the bcr/abl fusion in CML⁷, which is expressed only in tumor cells. In addition to this paradigm of specific tumor Ag, differentiation Ags, such as tyrosinase in melanoma, are transiently expressed in normal cells during their ontogeny³. Tumor induced by virus often express some viral Ags, like for example peptides of the oncoprotein E7 of the HPV16 virus in cervical uterus cancer⁴². From these examples it appears that the absence of tumor Ag is not, in many cases, the right explanation for an absence of or inefficient anti-tumor immune response.

Defect of Expression of MHC Molecules and of Antigenic Peptide Transport

As previously shown, antigenic peptide presentation by MHC molecules at the surface of APCs (class I for CD8⁺ cytotoxic lymphocytes, class II for the CD4⁺ auxiliary T cells) is necessary for their recognition by effector T lymphocytes. The class I MHC molecules consist of a membrane α -chain associated to a soluble β -chain, the β -2-microglobuline. The loss of the β -chain is responsible for the absence of expression of the α -chain at the APC surface, impairing the antigenic recognition. Many examples of loss or reduction of expression of the class I MHC molecules have been described in various tumors, such as head and neck carcinoma¹¹, prostate cancer⁴⁶, small cell lung cancer^{29, 43}, Burkitt's lymphoma⁴⁵, renal or colic carcinomas^{24, 25}. This expression of the class I molecules can be highly heterogeneous within the primitive tumor. For example, MHC class I molecule expression in melanoma clones is variable and correlates to their level of recognition by cytolytic lymphocytes⁴⁴. Still in melanoma, loss of expression of MHC class I molecules can occur after immunotherapy⁴⁴. The most immediate interpretation of this observation is that immunotherapy leads to a better recognition, and therefore destruction, of cells expressing MHC molecules, but is not able to eliminate the class I negative clones. Loss of expression of MHC class I molecules, in regard to the primary tumor, is also frequently observed in metastases^{11, 26}.

Defect of Expression of Adhesion/Costimulatory Molecules

Several couples of adhesion/costimulation molecules and their ligands such as LFA-1-ICAM-1, CD2-LFA-3 or CTLA-4/CD28-B7-1/B7-2 play an important role in the immune response. We will focus on this last system, which is central in tumor immune recognition^{20, 37, 38, 48}. The engagement of CD28 at the lymphocyte surface with its ligands B7-1 or B7-2 at the tumor cell surface provides to the T lymphocyte the second signal necessary to reach complete activation and IL-2 synthesis, in order to avoid anergy development. Solid tumors does not express B7-1 or B7-2²⁰. The situation is more complex in hematological neoplasms. The follicular and diffuse large cell lymphoma express B7-1 and B7-2 but at a very weak level, insufficient to allow efficient allogeneic immune recognition¹³. The so-called mantle-cell lymphoma or small lymphocytic lymphoma, as well as chronic lymphocytic leukemia (CLL), do not express B7-1 or B7-2^{13, 39, 55}. On the other hand, B7-1 is expressed at the surface of Reed-Sternberg cells in Hodgkin's disease, and contributes to their immune recognition^{12, 33}. In AMLs, B7-1 is in general very little expressed whereas B7-2 is readily present in particular in myelo/monocytic subtypes^{10, 23, 54}. The regulation of these molecules can also be aberrant. For example, the stimulation by interferon γ (IFN- γ) does not induce the expression of B7 molecules in the myelo/monocytic AMLs, in contrast to their "normal counterpart", the monocyte¹⁰. If the complete absence of B7 molecules does not allow the development of the immune response, some deleterious effects may also result from very low expression level. Indeed, the CTLA-4 molecule binds, like CD28, to B7-1 and B7-2, but has two major differences with regard to CD28: a higher affinity³¹ and the delivery of an inhibitory signal for the lymphocyte functions when CD28 is not committed at the same time¹⁷. If very few B7 molecules are available at the tumor cell surface, CTLA-4 may be stimulated without CD28 engagement, delivering therefore a message of negative regulation to the immune effector cells.

Tumor Cell Counterattack

Malignant cells can destroy or inactivate the effector cells, either by the secretion of soluble molecules (cytokines or soluble receptors) or by direct cellular contacts. The best illustration of this phenomenon is the "Fas counterattack"⁵⁰. Briefly, the Fas molecule, when

stimulated by his ligand (FasL), induces a message of active cell death or apoptosis. The Fas molecule is expressed by many cells, in particular by T lymphocytes. An expression of a functional FasL by tumor cells is frequent in colic carcinoma³⁵, hepatoma⁵¹, melanoma²¹ or lymphoma⁵⁸. Consequently, tumor infiltrating lymphocytes can be destroyed by apoptosis, whereas the tumor itself is often at least partially resistant to Fas-dependent apoptosis⁴⁰. The existence of increased circulating levels of soluble FasL in some hematological malignancies such as large granular lymphocyte lymphoma or natural killer (NK) lymphoma has been demonstrated⁵³. Other mechanisms of lymphocyte function inactivation have also been described, such as the inhibition of the CD40/CD40L system. The CD40 molecule is a member of the superfamily of tumor necrosis factor receptors (TNFR) and is expressed on many types of tumor cells^{4, 19}. The CD40/CD40L system plays a central role in the development of the immune response, establishing a reciprocal dialogue between T lymphocytes and the different types of APCs. The engagement of CD3/TcR by antigenic peptides presented by MHC quickly induces CD40L expression at the T lymphocyte surface. Then, CD40L binds to CD40 and induces or increases the expression at the tumor cell surface of various adhesion/costimulation molecules, such as B7-1, B7-2, LFA-3 or ICAM-1, which provide the second signal required to activate the naive T cells, amplify the immune response and prevent the induction of tolerance. Blood and splenic CD4⁺ lymphocytes from patients with CLL fail to express CD40L after activation by CD3⁶. The co-incubation of B cells from CLL patients with allogeneic T lymphocytes induces reduction of CD40L expression at the T cell surface. These data suggest therefore that CLL B lymphocytes inhibit the immune response by the suppression of the CD40-triggered T lymphocyte stimulation. Among the indirect mechanisms, the secretion by the tumor cells prostaglandin E2, transforming growth factor β , interleukin-10 or many other cytokines may contribute to T cell function inhibition³⁴.

How Can the Immune Response Bypass the Tumor Escape Mechanisms?

The immune system can also react in order to inhibit tumor development. Among the most interesting mechanisms are the so-called NK activity. The NK cells participate in the innate response against viruses, bacteria or tumor cells but, in contrast with B cells or T cells, without expressing Ag specific receptors (im-

munoglobulins or TcR) and without MHC restriction. The mechanism explaining the action of these cells is supported on the contrary by the "missing self hypothesis"³². Schematically, NK cells present on their surface receptors for MHC class I molecule, whose binding induces inactivation of their cytolytic functions. In the absence – or alteration – of MHC class I at the tumor cell membrane, the NK cells are not inactivated and therefore destroy the target cell. Finally, the neoplastic cells are kept between two antitumor mechanisms; if they express class I MHC molecules, they are susceptible to be destroyed by MHC-restricted specific T lymphocytes, while, if they lose their MHC class I determinants they become potential targets for the NK cells.

Various therapeutic interventions could contribute to improve the antitumor response, in particular by the increase of expression of adhesion molecules on the tumor surface. For example, the utilization of IL-2 in the AMLs increases blast cell expression of ICAM-1 and LFA-3³⁶. The IFNs²², but also some other cytokines still not used in human therapy such as IL-4⁹ or IL-7⁸ can also improve the immune recognition of the transformed cells. Recently, cancer cell stimulation by CD40 was shown to be highly efficient to restore immune response against weakly immunogenic tumors such as the follicular lymphoma (FL). The stimulation of FL cells by CD40 increases the expression of the adhesion/costimulation molecules B7-1, B7-2, ICAM-1 or LFA-3, and re-establish their recognition by allogeneic T lymphocytes⁴⁷. Once alloreactive T lymphocytes have been primed by the tumor cells stimulated by CD40, they are also capable of efficient recognition and destruction of cells from the same lymphoma even not stimulated by CD40⁴⁷. In addition, the reactivity and the possibilities of expansion of the tumor-infiltrating lymphocytes is greatly increased if they are incubated with FL pre-stimulated by CD40⁴⁹. Another potentially favourable effect of tumor cell triggering via CD40 is the induction of the expression MHC molecules as well as restoration of a functional antigenic peptide transport which both favour Ag presentation and recognition²⁷. The stimulation by CD40 could therefore be employed like an alternative strategy in order to increase the Ag-specific MHC-restricted antitumor response²⁷ in particular when other immunoregulatory cytokines such as IFNs are ineffective for instance in the Burkitt's lymphoma². Finally, an original mechanism by which the stimulation via CD40 could improve the immune recognition is the induction of cytokine secretion by tumor cells. For example, CD40 stimulation of Reed-Sternberg cells in Hodgkin's disease induces them to secrete

IL-8, IL-6, or TNF, which may play a role in the modulation of the immune response¹⁸ via chemoattraction and activation of monocytes or T lymphocytes, in addition to direct antitumor effects.

Perspectives

This overview has summarized some of the mechanisms used by tumor in order to escape the immune response, and the putative therapeutic possibilities to improve it. Nonetheless, some important mechanisms have not been discussed: a tumor growth potential exceeding the cytotoxic capacities of the T lymphocytes, tumor heterogeneity or its inaccessibility to the immune effectors, the variability in antigenic evolution, the resistance of the cancerous cells to the cytolysis, the limitation of T cell repertoire by the lymphocyte depletion induced by chemotherapy or radiotherapy. All these data would ideally be considered in immunotherapy protocols in order to optimise their efficiency.

Acknowledgment. The authors thank Dr. C. Mawas for helpful advice. This work was supported by the Groupement Entreprise Français Lutte Cancer, the Association pour la Recherche contre le Cancer, the Ligues contre le Cancer des Bouches-du-Rhône et du Var, the Fédération Nationale des Centres de Lutte Contre le Cancer, the Fondation Contre la Leucémie and the Institut National de la Santé et de la Recherche Médicale.

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Received in August 1998

Accepted in October 1998