



Review

Is Tumor Expression of the Major Histocompatibility Complex Antigen Required for T Cell Immune Surveillance?

YANG LIU* and PAN ZHENG

Department of Pathology, Ohio State University Medical Center, Columbus, OH 43210, USA

Abstract. Tumor expression of major histocompatibility complex antigen (MHC) class I and class II is not essential for the induction of memory T cells. However, induction of MHC class I-restricted effector cytotoxic T cells (CTL) appears dependent on MHC class I expression on tumors. Moreover, the effector function of tumor-specific CTL requires direct recognition of the tumor. In contrast, both the inductive and the effector phases of MHC class II-restricted T cells are independent of MHC class II expression on tumors.

Key words: tumor immunity; major histocompatibility complex; immune surveillance; antigen-presentation; cross-priming.

Introduction

The discovery of major histocompatibility complex (MHC) antigen can be credited in part to the study of tumor rejection antigens¹⁹. Given the fact that T cells, the major effector cells in cancer immunity, recognize antigenic peptides presented by the MHC molecules^{2, 6, 7, 9, 32}, it appears self-evident that tumor cells must express MHC antigen on the cell surface in order to be recognized by the T cells. Several recent discoveries in both the fundamental mechanisms of antigen presentation and the recognition of tumor and normal tissue by T cells, however, have made it necessary to re-evaluate this basic assumption. A reappraisal of this issue leads to several valuable lessons for the development of cancer vaccine and tumor immunotherapy.

Cross-Priming and the Induction of Effector vs Memory T Cells

T cells recognize antigenic peptide presented by the MHC. The majority of T cells that express $\alpha\beta$ T cell receptors (TCR) belong to one of two subsets: CD4⁺ T cells recognize antigens that have access to the endocytic pathway and are processed and presented in the endosomal compartment by MHC class II molecules. CD8 T cells, on the other hand, recognize antigens that are either synthesized or being delivered to the cytosol⁵. The intact proteins are degraded primarily by the proteasomes, and then the short peptides produced are transported to the endoplasmic reticulum (ER) by an ATP-dependent transporter. As a result, CD8 T cells primarily recognize intracellular antigens, and one may expect CD8 T cells to focus on the targets that have both MHC and the nominal antigen.

* Correspondence to: Dr. Yang Liu, Department of Pathology, Ohio State University Medical Center, 129 Hamilton Hall, 1645 Neil Avenue, Columbus, OH 43210, USA, tel.: +1 614 292 3054, fax: +1 614 688 8152, e-mail: liu-3@medctr.osu.edu

A notable exception was first documented in an elegant paper published almost 25 years ago. BEVAN⁴ demonstrated that, while the recognition of target cells by the cytotoxic T lymphocytes (CTL) was restricted by the MHC, the priming of CTL was restricted by the host MHC molecules, not by those on the cells that possessed the nominal antigens. He termed this phenomenon “cross-priming”. This paradoxical observation was reconciled when it was discovered that the host antigen-presenting cells (APC) can pick up extracellular antigens and process them by the MHC class I pathway¹⁷.

Due to cross-priming, one can probably extrapolate that, in the presence of APC, tumor cells may not need to express MHC class I in order to induce CTL. This is indeed the case as elucidated by HUANG et al.¹⁵, who were the first to demonstrate the normal priming of anti-tumor CTL with tumor variants that lacked cell surface MHC, an observation that we have extended to a plasmacytoma model involving a known antigen¹⁴. In order to determine whether the host APCs are essential for cross-priming, HUANG et al.¹⁵ lethally irradiated F1 mice and reconstituted them with the bone marrow of one parent. By studying the MHC-restriction of T cells primed in the chimeras, it was concluded that the bone marrow-derived cells were essential for the cross-priming. However, recent observations that the survival of naive T cells requires interaction with a restricting MHC element¹¹, perhaps on dendritic cells⁸, have made the conclusion of HUANG et al.¹⁵ less definitive. Nevertheless, the critical involvement of host APC is substantiated by the observation that expression of the costimulator B7 on host APC is required for the induction of anti-tumor CTL, regardless of B7 expression on the tumor cells²¹.

As a minimal model, one could argue that tumor cells are mere donors of the nominal antigens, and that immature host dendritic cells (DC) infiltrate the tumor, take up tumor antigen, and differentiate into mature DC as they return to the lymphoid tissue. This hypothesis is consistent with the recent analysis of tumor-infiltrating DC²⁵. This being the case, why would expression of B7 molecules on the tumor cells enhance the induction of anti-tumor CTL response, as many groups have documented^{3, 10, 23, 27}? WU et al.²⁹ suggested that B7 expressed on tumors promotes natural killer (NK) cell lysis of tumor cells, and the apoptosis of tumor cells facilitates the uptake of tumor antigen by the host APC. In addition to the lack of direct supporting evidence, this model is also challenged by the observation that necrotic, but not apoptotic cells induce DC maturation¹², which is considered essential for CTL priming. However, some groups have reported that apoptotic

cells are efficiently processed by DC to stimulate T cells¹.

The need to express B7 molecules on tumors in order to induce anti-tumoral immunity suggests that tumors may directly stimulate their specific T cells. An alternative interpretation for the need to improve the costimulatory activity of tumor cells involves a clearer definition of the type of CD8 T cells, either memory or effector, that are produced after T cell priming. A successful activation of T cells yields both effector and memory T cells. An effector T cell kills tumor cells without further activation. A memory cell, on the other hand, lacks cytotoxicity, but can become an effector shortly after restimulation. We and others have reported distinct requirements for the induction of memory vs effector T cells, including costimulatory molecules²⁰, TCR ligand affinity¹³ and the location of production^{14, 21}. Since most of the previous studies regarding the requirement for MHC expression on tumors uses recall response as the readout, it is most likely that the lack of an active role of tumor cells in T cell priming reflects that of memory T cell induction. We have recently tested this hypothesis using tumor variants that lack MHC class I and/or costimulatory molecules. We observed that, while the induction of memory cells does not require MHC expression on the tumor cells, such a requirement was readily demonstrated when the effector cells were measured¹⁴. It is possible that the TCR ligand density produced by the cross-presentation pathway is somewhat lower than that produced by direct presentation. As such, only memory T cells are induced in the absence of direct antigen presentation. While this observation is yet to be substantiated in other tumor models, this alternative hypothesis would reconcile the apparent CTL priming by MHC class I[−] tumors and the fact that improved costimulation by the tumor's cells would increase its immunogenicity.

Requirement of MHC Expression for Tumor Rejection

Direct interaction between tumor-specific T cells and tumor cells requires recognition of MHC molecules on the tumor cells. The issue of whether tumor cells need to express MHC in order to be rejected by the T cells can be rephrased as to whether T cells need to recognize tumor cells directly in order to reject tumors. Schreiber and colleagues demonstrated that an MHC class II-restricted CD4 T clone that recognizes a tumor-specific antigen is sufficient to cause tumor rejection without the participation of other subsets of antigen-

-specific lymphocytes. The rejection can be substituted in part by interferon γ , and requires the response of non-lymphocytes in the host to interferon γ ²².

The ability of CD4 T cells to reject MHC class II⁻ tumor cells is reminiscent of studies in the pathogenesis of autoimmune diabetes and experimental autoimmune encephalomyelitis. Lafferty and colleagues demonstrated that autoreactive CD4 T cells alone are capable of destroying Langerhans' β -islet cells despite of their lack of MHC class II²⁸. This notion is supported by observations that transgenic mice expressing TCR restricted by MHC class II develop spontaneous, organ-specific autoimmune diseases even when the cells that are destroyed are devoid of MHC class II^{16, 18}. Since CD4 T cells can not recognize the target cell directly, the tissue destruction is most likely caused by the local inflammatory response.

CD8 T cells are the major effector cells in tumor rejection. Because of the ability of host APC to cross-process antigens released from tumors, one may predict that CD8 T cells may reject MHC class I⁻ deficient tumors. However, to our knowledge, no evidence has been published that has conclusively demonstrated that CD8 T cells can reject MHC class I⁻ tumors. On the contrary, we have demonstrated in mice, which have potent anti-tumor CTL response, that tumors can recur by down-regulation of cell surface MHC class I via malfunction of proto-oncogene PML³⁰. Most strikingly, in some recurrent tumors we can observe co-existence of MHC class I^{low} tumor cells and effector cytotoxic T cells³¹. In this regard, it should be pointed out that down-regulation of MHC class I is widely observed among malignant human cancers²⁴. The ability of tumors to evade CTL recognition by shutting down cell surface MHC class I expression makes a strong argument that tumors need to express MHC class I for their rejection by CD8 T cells.

Concluding Remarks

In summary, the requirement of tumor expression of MHC molecules for immune surveillance by T cells appears to vary depending on the class of MHC molecules and, consequently, the subset of T cells involved (Table 1). Most tumor cells lack MHC class II, but can be recognized by MHC class II restricted T cells. Limited studies indicate that CD4 T cells may reject class II⁻ tumors. For CD8 T cell responses, it is likely that MHC class I expression on tumor cells may not be required for the priming of memory T cells, although an optimal induction of effector T cells appears to be

Table 1. Requirement for tumor expression of MHC for their recognition by T cells (tentative conclusions)

	MHC class II/CD4 T cells	MHC class I/CD8 T cells
Induction		
memory	no	no
effector	no	yes
Rejection	no	yes

dependent of MHC class I on the tumor cells. Rejection of tumors by CD8 T cells, however, requires MHC class I expression. These basic principles suggest that, for tumors that share the same antigens, one can design a tumor vaccine across the MHC barrier as long as the host can present some portions of the antigens by the MHC class I pathway. Moreover, there has been a renewal of interest in the identification of MHC class II-restricted tumor antigens²⁶. Stimulating tumor specific CD4 T cells may induce a protective immunity even if the tumor cells are devoid of MHC class II. As such, tumors will not be able to evade T cell recognition by disabling their MHC class II antigen-presentation machinery.

Acknowledgment. We thank Jennifer Kiel for secretarial assistance. This study is supported by grants from National Institute of Health USA (CA58033, AI32981, CA69091, and CA82355).

References

1. ALBERT M. L., SAUTER B. and BHARDWAJ N. (1998): Dendritic cells acquire antigen from apoptotic cells and induce class I-restricted CTLs. *Nature*, **392**, 86–89.
2. BABBITT B. P., ALLEN P. M., MATSUEDA G., HABER E. and UNANUE E. R. (1985): Binding of immunogenic peptides to Ia histocompatibility molecules. *Nature*, **317**, 359–361.
3. BASKAR S., OSTRAND-ROSENBERG S., NABAVI N. and GLIMCHER L. (1993): Constitutive expression of B7 restores immunogenicity of tumor cells expressing truncated MHC class II molecules. *Proc. Natl. Acad. Sci. USA*, **90**, 7015–7019.
4. BEVAN M. J. (1976): Cross-priming for a secondary cytotoxic response to minor H antigens with H-2 congenic cells which do not cross-react in the cytotoxic assay. *J. Exp. Med.*, **143**, 1283–1288.
5. BEVAN M. J. (1987): Antigen recognition. Class discrimination in the world of immunology (news). *Nature*, **325**, 192–194.
6. BJORKMAN P. J., SAPER M. A., SAMRAOUI B., BENNETT W. S., STROMINGER J. L. and WILEY D. C. (1987): The foreign antigen binding site and T cell recognition region of class I histocompatibility antigens. *Nature*, **329**, 512–518.
7. BLANDEN R. V., DOHERTY P. C., DUNLOP M. B., GARDNER I. D., ZINKERNAGEL R. M. and DAVID C. S. (1975): Genes required for cytotoxicity against virus-infected target cells in K and D regions of H-2 complex. *Nature*, **254**, 269–270.
8. BROCKER T. (1997): Survival of mature CD4 T lymphocytes is

- dependent on major histocompatibility complex class II-expressing dendritic cells. *J. Exp. Med.*, **186**, 1223–1232.
9. BUUS S., SETTE A., COLON S. M., MILES C. and GREY H. M. (1987): The relation between major histocompatibility complex (MHC) restriction and the capacity of Ia to bind immunogenic peptides. *Science*, **235**, 1353–1358.
 10. CHEN L., ASHE S., BRADY W. A., HELLSTROM I., HELLSTROM K. E., LEDBETTER J. A., MCGOWAN P. and LINSLEY P. S. (1992): Costimulation of antitumor immunity by the B7 counterreceptor for the T lymphocyte molecules CD28 and CTLA-4. *Cell*, **71**, 1093–1102.
 11. FREITAS A. A. and ROCHA B. (1999): Peripheral T cell survival. *Curr. Opin. Immunol.*, **11**, 152–156.
 12. GALLUCCI S., LOKEMA M. and MATZINGER P. (1999): Natural adjuvants: endogenous activators of dendritic cells. *Nat. Med.*, **5**, 1249–1255.
 13. GOLDRATH A. W. and BEVAN M. J. (1999): Low-affinity ligands for the TCR drive proliferation of mature CD8⁺ T cells in lymphopenic hosts. *Immunity*, **11**, 183–190.
 14. GUILLoux Y., BAI X., LIU X., ZHENG P. and LIU Y. (2001): Optimal induction of effector but not memory anti-tumor cytotoxic T lymphocytes involves direct antigen presentation by the tumor cells. *Cancer Res.*, **61**, 1107–1112.
 15. HUANG A. Y., GOLUMBEEK P., AHMADZADEH M., JAFFEE E., PARDOLL D. and LEVITSKY H. (1994): Role of bone marrow-derived cells in presenting MHC class I-restricted tumor antigens. *Science*, **264**, 961–965.
 16. KATZ J. D., WANG B., HASKINS K., BENOIST C. and MATHIS D. (1993): Following a diabetogenic T cell from genesis through pathogenesis. *Cell*, **74**, 1089–1100.
 17. KOVACSOVICS-BANKOWSKI M. and ROCK K. L. (1995): A phagosome-to-cytosol pathway for exogenous antigens presented on MHC class I molecules. *Science*, **267**, 243–246.
 18. LAFAILLE J. J., NAGASHIMA K., KATSUKI M. and TONEGAWA S. (1994): High incidence of spontaneous autoimmune encephalomyelitis in immunodeficient anti-myelin basic protein T cell receptor transgenic mice. *Cell*, **78**, 399–408.
 19. LITTLE C. C. (1924): The genetics of tissue transplantation in mammals. *Cancer Res.*, **8**, 75–95.
 20. LIU Y., WENGER R. H., ZHAO M. and NIELSEN P. J. (1997): Distinct costimulatory molecules are required for the induction of effector and memory cytotoxic T lymphocytes. *J. Exp. Med.*, **185**, 251–262.
 21. MARIC M., ZHENG P., SARMA S., GUO Y. and LIU Y. (1998): Maturation of cytotoxic T lymphocytes against a B7-transfected nonmetastatic tumor: a critical role for costimulation by B7 on both tumor and host antigen-presenting cells. *Cancer Res.*, **58**, 3376–3384.
 22. MUMBERG D., MONACH P. A., WANDERLING S., PHILIP M., TOLEDANO A. Y., SCHREIBER R. D. and SCHREIBER H. (1999): CD4(+) T cells eliminate MHC class II-negative cancer cells *in vivo* by indirect effects of IFN-gamma. *Proc. Natl. Acad. Sci. USA*, **96**, 8633–8638.
 23. RAMARATHINAM L., CASTLE M., WU Y. and LIU Y. (1994): T cell costimulation by B7/BB1 induces CD8 T cell-dependent tumor rejection: an important role of B7/BB1 in the induction, recruitment, and effector function of antitumor T cells. *J. Exp. Med.*, **179**, 1205–1214.
 24. SELIGER B., MAEURER M. J. and FERRONE S. (1997): TAP off-tumors on. *Immunol. Today*, **18**, 292–299.
 25. SOMMERS C. L., RABIN R. L., GRINBERG A., TSAY H. C., FARBER J. and LOVE P. E. (1999): A role for the Tec family tyrosine kinase Txk in T cell activation and thymocyte selection. *J. Exp. Med.*, **190**, 1427–1438.
 26. TOES R. E., OSSENDORP F., OFFRINGA R. and MELIEF C. J. (1999): CD4 T cells and their role in antitumor immune responses. *J. Exp. Med.*, **189**, 753–736.
 27. TOWNSEND S. E. and ALLISON J. P. (1993): Tumor rejection after direct costimulation of CD8⁺ T cells by B7-transfected melanoma cells. *Science*, **259**, 368–370.
 28. WANG Y., PONTESILLI O., GILL R. G., LA ROSA F. G. and LAFERTY K. J. (1991): The role of CD4⁺ and CD8⁺ T cells in the destruction of islet grafts by spontaneously diabetic mice. *Proc. Natl. Acad. Sci. USA*, **88**, 527–531.
 29. WU T. C., HUANG A. Y., JAFFEE E. M., LEVITSKY H. I. and PARDOLL D. M. (1995): A reassessment of the role of B7-1 expression in tumor rejection. *J. Exp. Med.*, **182**, 1415–1421.
 30. ZHENG P., GUO Y., NIU Q., LEVY D. E., DYCK J. A., LU S., SHEIMAN L. A. and LIU Y. (1998): Proto-oncogene PML controls genes devoted to MHC class I antigen presentation. *Nature*, **396**, 373–376.
 31. ZHENG P., SARMA S., GUO Y. and LIU Y. (1999): Two mechanisms for tumor evasion of preexisting cytotoxic T-cell responses: lessons from recurrent tumors. *Cancer Res.*, **59**, 3461–3467.
 32. ZINKERNAGEL R. M. and DOHERTY P. C. (1974): Restriction of *in vitro* T cell-mediated cytotoxicity in lymphocytic choriomeningitis within a syngeneic or semiallogeneic system. *Nature*, **248**, 701–702.

Received in December 1999

Accepted in March 2000