Resistance to Lysis by Cytotoxic T Cells: A Dominant Effect in Metastatic Mouse Prostate Cancer Cells

Hon-Man Lee, Terry L. Timme, and Timothy C. Thompson

ABSTRACT

Better understanding of the immunology of prostate cancer is needed for the development of new therapeutic approaches that can be used in conjunction with current treatment methods. The present study was designed to compare the immunological properties of a genetically matched pair of primary tumor- and metastasis-derived prostate cancer cell lines generated from the mouse prostate reconstitution (MPR) model. Only the primary prostate cancer cells were immunogenic in that prior immunization with irradiated primary but not the metastatic prostate cancer cells delayed the growth of subsequently injected live cancer cells. The lack of immunogenicity of the metastatic cells was not attributable to their inability to induce antitumor cytotoxic T cells. Both primary and metastatic cells induced antitumor CTLs in syngeneic hosts, but unlike the primary cells, the metastatic cells were resistant to CTL lysis. Differential resistance to cytolysis in metastatic versus primary prostate cancer cells was not attributable to the differential expression of molecules such as transporter associated with antigen processing (TAP)-1, TAP-2, low molecular weight protein of the proteasome complex (LMP)-2, and LMP-7 that contribute to antigen presentation by class I MHC. IFN-γ induced surface class I MHC expression, as well as gene expression of TAP-1, TAP-2, LMP-2, and LMP-7 in the metastatic cells, but the cells remained resistant to cell lysis induced by CTLs. Interestingly, although in comparison to the primary cells the metastatic cells were resistant to cytolysis, both cell types were susceptible to DNA fragmentation induced by CTLs. Cell fusion between primary and metastatic cancer cells resulted in hybrids that also resisted the cytolytic activity of CTLs. Therefore, there is a dominant factor(s) in the metastatic prostate cancer cells that confers specific protection against CTL cytolysis in this model system.

INTRODUCTION

Prostate cancer is now the most commonly diagnosed cancer in men and leads to tens of thousands of deaths every year (1). Current curative treatment options are only applicable to patients with disease that is localized to the prostate, and there is a need to develop new therapies that can more effectively control both local and metastatic disease. Determination of the molecular basis of prostate cancer progression and development of new therapeutic approaches require studies in suitable model systems. Our laboratory has developed a unique prostate cancer model, the MPR model (2). Urogenital sinus tissues isolated from 17-day-old mouse fetuses are transduced with the ras and myc oncogenes via a replication-deficient recombinant retrovirus. Infected cells are then grafted under the renal capsule of syngeneic adult male hosts where primary carcinomas arise within the reconstituted prostate (2). When ras and myc are transduced into p53 null urogenital sinus tissues, the resulting primary tumors are metastatic with organ specificity that closely resembles human disease (3).

The relevance of this model has been supported by clinical studies demonstrating mutation or aberrant activities of ras (and downstream signal transduction components), myc, and p53 in human prostate cancer (4–8). Genetically matched pairs of primary and metastatic cell lines have been generated from primary tumors and their spontaneous metastases from these MPR animals (3). Recent studies have demonstrated that orthotopic tumors produced by metastasis-derived cell lines tend to grow less rapidly but exhibit greater spontaneous metastatic potential than their matched cell line counterparts derived from the primary tumor (9). Overall, this cell line-based model system of prostate cancer is highly suitable for determining the unique characteristics of the metastatic phenotype.

Progressive tumor growth impairs immune responses in the host (10), but at present the interaction between prostate cancer cells and the host immune system during cancer progression and therapy is not well defined. Determining the nature of immune responses against prostate cancer cells would facilitate further understanding of the mechanism(s) of tumor progression and may lead to the development of more effective treatments for the disease. We used genetically matched pairs of primary tumor-derived and metastasis-derived cell lines generated from the MPR model to determine whether there are differential immune responses against the cancer cells with respect to tumor site derivation/metastatic potential. The results of this study indicate that both primary and metastatic prostate cancer cells have similar capacities to induce antitumor CTLs, but the metastatic cells are resistant to cytolysis induced by CTLs. The resistant trait appears to be dominant because hybrids of primary and metastatic cancer cells are also resistant to CTL lysis. Interestingly, the metastatic cancer cells remain susceptible to DNA fragmentation induced by CTLs. Data reported in this study thus provide evidence that one of the mechanisms for enhancing tumor metastasis is by the acquisition of a dominant resistant phenotype against CTL cytolysis.

MATERIALS AND METHODS

Animals and Prostate Tumor Cell Lines. BALB/c and C56BL/6 mice were purchased from Harlan Sprague Dawley (Houston, TX) and The Jackson Laboratory (Bar Harbor, ME), respectively. 129/Sv mice were maintained at our facility. Prostate cancer cell lines were generated from 129/Sv mice using the MPR model system (3). Primary prostate cancer cell line 148-1 PA (PA, also designated 1A) and metastatic cancer cell line 148-1 LMD (LMD), both derived from animal designated 148-1, were found to originate from the same clone (3). Cancer cells were grown in DMEM with 10% fetal bovine serum, and cultures were passaged by trypsinization with 0.025% trypsin. Cell passages 8–10 were used in experiments reported here. All mice were maintained in facilities approved by the American Association for Accreditation of Laboratory Animal Care, and all animal studies were conducted in accordance with the principles and procedures outlined in the NIH’s Guide for the Care and Use of Laboratory Animals.

Reagents. IL-2 and IFN-γ were purchased from Genzyme (Cambridge, MA). T-cell enrichment columns and anti-TCF-β were purchased from R&D Systems (Minneapolis, MN). Antibodies for flow cytometry were purchased from PharMingen (San Diego, CA). Anti-Thy1.2 hybridoma (30-H12) was obtained from American Type Culture Collection. Rabbit complement was purchased from Accurate Chemical (Westbury, NY). Mitomycin C was purchased from Sigma. Probes for Northern blots of LMP-2, LMP-7, TAP-1, and
of Class I MHC expression on primary and metastatic prostate tumor cells

### Table 1

<table>
<thead>
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<th>IFN-γ (units/mL)</th>
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<td>10.08 (96%)</td>
<td>86.23 (100%)</td>
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<td>50</td>
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<td>11.55 (92%)</td>
<td>107.8 (99%)</td>
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</table>

**TAP-2 were kindly provided by Dr. John Monaco (University of Cincinnati, Cincinnati, OH).**

**Immunogenicity of PA and LMD Tumor Cells.** Fifty thousand PA or LMD prostate cancer cells were injected s.c. into normal 129/Sv male mice, 12 weeks of age, or into mice immunized s.c. with 5 × 10⁶ irradiated PA or LMD cells 2 weeks earlier. Tumor volume was calculated by the formula of a rotational ellipsoid: (m₁² × m₂ × 0.5236), where m₁ represents the shorter axis and m₂ the longer axis (11).

**Induction of CTL in Vivo.** BALB/c mice were injected s.c. with 5 × 10⁵ irradiated (35,000 rads) PA cells. Two to three weeks after injection, spleen cells from primed mice were cultured (8 × 10⁵ cells/well) with mitomycin C-treated cancer cells (5 × 10⁵ cells/well) for 6 days in 24-well plates. IL-2 (20 units/ml) and/or anti-TGF-β (30 μg/ml) were added on day 0, and additional IL-2 (20 units/ml) was added on days 2 and 4. For the induction of CTLs in syngeneic hosts, 129/Sv mice were injected s.c. with 5 × 10⁵ irradiated PA or LMD cells (35,000 rads) on days 0 and 8. Twelve days after the last immunization, spleen cells from injected mice were cultured (7 × 10⁶ cells/well) with mitomycin C-treated PA or LMD cells (6 × 10⁵ cells/well) in the presence of anti-TGF-β (30 μg/ml) for 5 days. IL-2 (20 units/ml) was added on day 2.

**Cytolysis of PA and LMD Cells by CTLs.** Effector CTLs were either induced in vivo as described above or generated in vitro by stimulating T-cell-enriched BALB/c spleen cells with T-cell-depleted C57BL/6 or 129/Sv spleen cells for 5 days in 24-well plates. PA or LMD cancer cells that had been incubated with or without 100 units/ml IFN-γ for 2 days were used as target cells in cytolytic assays. Target cells labeled with [⁵¹Cr]chromium were used in standard [⁵¹Cr]chromium release assays to determine cell lysis, whereas target cells labeled with 5 μCi/ml of [¹³⁵I]thymidine overnight were used in DNA fragmentation assays as described (12).

**Northern Blot Analysis.** PA or LMD cells were incubated with or without 100 units/ml IFN-γ for 2 days, and total RNA was isolated by Ultraspec RNA (Biotex, Houston, TX). RNA was separated on a 1% SeaKemGT agarose gel by electrophoresis and transferred to nitrocellulose as described previously (3). The membranes were first probed with LMP-2, LMP-7, TAP-1, or TAP-2, stripped, and reprobed with glyceraldehyde-3-phosphate dehydrogenase as control.

**Cell Fusion Studies.** PA or LMD cells were transfected with plasmids conferring resistance to puromycin or hygromycin. Transfected cells were then fused with polyethylene glycol and selected in DMEM containing 10% FCS, 25 μg/ml puromycin, and 600 μg/ml hygromycin. Double-resistant hybrid cells were collected and used as target cells for allogeneic CTLs derived from C57BL/6-stimulated BALB/c T cells.

### RESULTS

**Immunogenicity of Primary and Metastatic Mouse Prostate Cancer Cells.** Tumor cells can evade immune responses through reduced expression of tumor antigens; alternatively, tumor antigens may not be presented to T cells because of defective MHC expression. To explore the possibility of differential immunogenicity in primary tumor-derived mouse prostate cancer cells compared with their metastasis-derived counterparts, surface MHC expression was first examined by flow cytometry in a pair of MPR primary and metastatic cancer cell lines (Table 1). In terms of mean fluorescence intensity, primary prostate cancer cells (PA) had almost 3-fold higher class I MHC expression than the metastatic prostate cancer cells (LMD). However, class I MHC expression was increased in both cell lines after treatment with IFN-γ, a potent inducer of class I MHC expression. Thus, although MHC expression on LMD cells was relatively lower than that of PA cells after IFN-γ treatment, MHC expression was responsive to up-regulation in the metastatic cells. On the other hand, class II MHC was not expressed on either cell line before or after treatment with IFN-γ. Similar results were obtained from two other pairs of similarly derived primary and metastatic mouse prostate cancer cell lines (data not shown).

Immunogenicity of the primary and metastatic mouse prostate cancer cells was examined using the immunization and challenge experiment. Syngeneic 129/Sv hosts were immunized with irradiated PA or LMD cells by s.c. injection. Immunized animals were then challenged 2 weeks later with s.c. injected live cancer cells of the same type. An immunogenic tumor would induce antitumor immunity that inhibits the growth of the challenge tumor. As shown in Fig. 1, the growth of PA cells was inhibited at early time points in immunized animals, whereas prior immunization with LMD had no effect on the growth of the subsequently injected LMD cells. Hence, primary cancer cells, but not metastatic prostate cancer cells, were immunogenic in this assay.

**Role of TGF-β in the Induction of Antitumor CTLs.** The above results indicate that PA and LMD cells evoke different immune responses; however, these experiments did not address whether there is differential reaction in the induction phase and/or the effector phase of CTL activities. Initial attempts to induce antitumor CTLs by coculture of spleen cells and cancer cells were unsuccessful. Because these cancer cells secrete a significant amount of TGF-β, we tested whether cancer cell-derived TGF-β may inhibit the generation of CTLs. To examine the effect of TGF-β in the induction of antitumor CTLs, spleen cells from allogeneic BALB/c mice immunized with s.c. injection of irradiated PA cells were restimulated in vitro in the presence or absence of anti-TGF-β antibody. The resulting effec-
tor cells were tested in the CTL assay using IFN-γ-treated PA cells as targets (IFN-γ-treated tumor cells are better target cells, as shown below). Results in Fig. 2 show that minimal CTL activities were generated in the presence or absence of exogenous IL-2, whereas the addition of anti-TGF-β antibody led to a high level of CTL activities. These results thus demonstrated a role of cancer cell-derived TGF-β in suppressing CTL induction in vitro. Consequently, anti-TGF-β antibody was added to all subsequent cocultures of spleen cells and prostate cancer cells.

**Induction of Syngeneic and Allogeneic Antitumor CTLs.** The differential immunogenicity reported above suggests that PA and LMD cells may have different capacities in inducing CTL responses. To address this issue, antitumor CTL activities were examined in syngeneic mice immunized with irradiated PA or LMD cells. Effector CTLs were then tested on target cells treated with or without IFN-γ. As shown in Fig. 3, immunization with both PA and LMD cells induced CTLs that had lytic activities on PA target cells, especially on PA cells that had prior IFN-γ treatment. These results indicated that both primary and metastatic cancer cells are capable of inducing antitumor CTLs, and incubation with IFN-γ makes the cancer cells more susceptible to CTL lysis. However, the same CTLs were not effective against LMD target cells, regardless of IFN-γ treatment. Thus, the apparent lack of immunogenicity in LMD cells is not attributable to the inability to induce CTL responses; rather, the metastatic cells are resistant to cytolysis.

The susceptibility of PA and LMD cells to CTL lysis was further tested in an allogeneic system. Effector CTLs generated from C56Bl/6-stimulated BALB/c T cells were tested on cancer cell targets incubated with or without IFN-γ. Compared with significant lysis of PA cells, there was only minimal lysis of LMD cells (Fig. 4). Incubation with IFN-γ led to enhanced lysis of both PA and LMD cells; nevertheless, lysis of LMD cells was still significantly lower than that of PA cells. Therefore, even after a high level of class I MHC expression was induced, the metastatic cancer cells remained relatively resistant to CTL lysis. Taken together, these data indicate that differential immune activities to PA and LMD cells were attributable largely to the differences in the effector phase of CTL response.

**Characterization of Resistance to CTL Lysis.** Defective expression of class I antigen processing machinery has been reported in metastatic human prostate cancer cells and renal carcinoma cells (14, 15), thus raising a possible explanation for the differential immune responses against PA and LMD cells reported here. We thus examined the gene expression of antigen processing components including TAPs (TAP-1 and TAP-2) and the LMPs (LMP-2 and LMP-7) in PA and LMD cells. Total RNA was isolated from PA and LMD cells after being cultured in the presence or absence of IFN-γ for 2 days. As shown in Fig. 5, there was no significant differential expression in PA versus LMD cells. Neither cell line expressed TAP-1, TAP-2, LMP-2, or LMP-7 constitutively, but a high level of gene expression was induced by IFN-γ in both PA and LMD cells. Therefore, a high level of gene expression for the antigen presentation components, as well as
class I MHC surface expression, was induced by IFN-γ in LMD cells, yet the cancer cells remained resistant to CTL lysis. These data thus indicate that the resistant phenotype is independent of class I MHC expression.

Because LMD cells secreted a higher level of TGF-β than PA cells, it was of interest to examine whether target cell-derived TGF-β would interfere with the activities of effector CTLs. As shown in Fig. 6, addition of up to 100 μg/ml of anti-TGF-β antibody did not have a significant effect on allogeneic CTL responses against PA or LMD cells. To further address whether the metastatic cancer cells resist CTL lysis by secretion of soluble inhibitory factors, the effect of conditioned culture medium from PA or LMD cells on CTL activities was examined. Lytic activities on PA target cells were not affected by the addition of culture supernatant from either PA or LMD cells (Fig. 7), top). Therefore, it seems unlikely that resistance to cytolysis is the result of differential secretion of TGF-β or other inhibitory factors.

The metastatic cancer cells may resist CTL lysis by evading recognition and binding to effector CTLs. We thus performed a cold target competition assay to determine whether there was a difference in cell-cell contact between the cancer cells and effector CTLs. Unlabeled PA cells effectively competed for CTL recognition and inhibited lysis on labeled PA cells in a dose-dependent manner (Fig. 7, bottom panel). Addition of unlabeled LMD cells also led to similar level of lysis inhibition, indicating that effector CTLs had a comparable level of cellular interaction with the PA or LMD cells. P815 cells, which are syngeneic to the effector CTLs, were added as control and did not inhibit lysis on the primary cancer cells. Therefore, these data do not support the notion that the metastatic cancer cells resist cytolytic activities by evading recognition by effector CTLs.

Effector CTLs destroy target cells by inducing rapid apoptosis, followed by cell lysis and cell death. The extent of cell lysis and DNA fragmentation induced by CTLs were examined in PA and LMD cells (Fig. 8). Compared with PA cells, LMD cells treated with or without IFN-γ resisted cell lysis by CTLs; however, a significant and high level of DNA fragmentation was induced in both cell types. Although LMD cells sustained substantial level of DNA damage induced by the CTLs, they remained highly resistant to lysis by CTLs. These results indicated that cell death and apoptosis signals were transmitted to the cancer cells, yet the metastatic cancer cells resisted cytolitic activities induced by CTLs.

To further characterize the genetic basis of cytolysis resistance in LMD cells, the susceptibility of PA and LMD cell hybrids to CTL lysis was examined. Puromycin- or hygromycin-resistant PA or LMD cells were polyethylene glycol fused, and double-resistant hybrid cells were selected and used as target cells for allogeneic CTLs generated...
CTL LYSS RESISTANCE IN METASTATIC PROSTATE CANCER

DISCUSSION

In this report, we have examined the immunological properties of a pair of primary tumor- and metastasis-derived mouse prostate cancer cell lines in the induction and effector phases of CTL responses. These prostate cancer cell lines are clonally related and have been used extensively as a model for metastatic prostate cancer in our laboratory. Results reported above indicate that there were differential immune responses to these cells. Primary (PA) and metastatic prostate cancer cells (LMD) had significant functional differences, specifically at the effector phase of CTL cytolysis. Immunization with both irradiated PA and LMD cells induced CTL activities in syngeneic hosts. The PA cells were modestly susceptible to CTL lysis; however, they became highly susceptible to CTL lysis when a high level of class I MHC expression was induced. On the contrary, LMD cells were resistant to CTL lysis, although similar levels of DNA fragmentation was induced in both cell types. Resistance to CTL lysis was dominant because cell hybrids of PA and LMD were also resistant to cytolysis. Therefore, these results suggest that prostate cancer cells acquire a phenotype that confers protection against CTL lysis as the tumor cells progress and metastasize. Further characterization of this phenotype may provide insight into prostate cancer progression and possibly lead to new targets for therapeutic intervention.

One of the mechanisms for the immune escape phenotype in tumor cells is loss or reduction of class I MHC expression (16–18). LMD cells expressed reduced levels of cell surface class I MHC compared with PA cells. Defective class I MHC expression has been attributed to functional deficiencies of the genes of the antigen-processing machinery (14, 15). Suppression of TAP-2 gene expression in one human metastatic prostate tumor cell line resulted in loss of class I MHC expression. IFN-γ restored class I MHC expression and function in that cell line by enhancing the expression of TAP-2 (14). In metastatic renal tumor cells, a decrease in class I MHC expression was associated with reduced TAP-1, TAP-2, LMP-2, and LMP-7 expression, as well as decreased antigen transporter function (15). Data presented in this report indicate that class I MHC was expressed on the surface of the prostate cancer cells in the absence of mRNA expression for TAP-1, TAP-2, LMP-2, and LMP-7. IFN-γ induced expression of these four antigen-processing molecules and enhanced class I MHC expression on both PA and LMD cells. This is in agreement with other studies that show a relationship between class I MHC expression and gene expression for antigen presentation (19, 20). However, class I MHC expression did not play a major role in the

from C57BL/6-stimulated BALB/c T cells (Fig. 9). In contrast to a significant level of lysis on PA parental cells, cell hybrids derived from two independent fusions of PA and LMD were resistant to CTL lysis. There were only low levels of lysis on the fused cells and parental LMD cells. Resistance to lysis in the fused cells was not overcome by IFN-γ, because lysis on IFN-γ-treated hybrid cells was still significantly lower than that on similarly treated PA parental cells. Hence, these results suggest the presence of dominant factor(s) in metastatic mouse prostate cancer cells that confers protection to CTL lysis.
differential responses to CTL cytolysis. IFN-γ-treated PA cells became highly susceptible to CTL lysis, whereas similarly treated LMD cells expressing a high level of class I MHC remained resistant to CTL killing. Thus, resistance to CTL cytolysis was independent of class I MHC expression.

The apparently dominant phenotype of cytolysis resistance in LMD cells is intriguing. Compared with their nonmetastatic counterparts, LMD cells were more resistant to lysis induced by CTLs. Cell hybrids between PA and LMD cells were also resistant to CTL cytolysis. It has been reported that tumor cells may acquire mechanisms to suppress apoptosis as they progress and metastasize. A metastatic variant of the LNCaP human prostate carcinoma line was more resistant to apoptosis than the nonmetastatic variant. Apoptosis resistance was associated with higher levels of expression of the cell death suppressor BCL-2 and lower levels of the death promoters BAX and BAK (21). Moreover, apoptosis resistance can be regulated by a dominant apoptosis suppressor factor (22). Cell hybrids between apoptosis-resistant and apoptosis-sensitive human prostate cancer cell lines were found to be also resistant to Fas- and tumor necrosis factor-mediated apoptosis. Presumably, the inhibitory protein that suppresses apoptosis in Fas-resistant cell lines acts at the apex of the apoptosis cascade by preventing the activation of caspase-8 (23). A lymphoid-specific apoptosis regulator that inhibited apoptosis mediated by members of the TNF receptor family also inhibited the processing of caspase-8 (24). However, the cell death pathways induced by cytotoxic T cells and the mechanism of resistance to the cytotoxic activities of CTLs demonstrated here may be different from these studies. CTLs can destroy target cells through one of two major pathways, i.e., the perforin/granzyme pathway and the Fas pathway (25). CTLs derived from mice deficient in Fas ligand have no measurable defect in cytolysis against allogeneic target cells (26), and target cell killing mediated by allospecific CD8+ CTLs is nearly completely dependent on the perforin/granzyme pathway (25). Therefore, cytotoxic activities reported in this study were most likely mediated through the perforin/granzyme pathway. This is further supported by the finding that showed a minimal level of Fas surface expression on the cancer cells we used, and anti-Fas antibody induced <10% of DNA fragmentation (data not shown). We presented evidence indicating that metastatic mouse prostate cancer cells resisted cell lysis but not DNA fragmentation. It seems unlikely that resistance to cytolysis is attributable to a defect in cellular interaction between effector CTL and cancer cells. PA and LMD cells competed equally well for CTL recognition and inhibited CTL activities to a similar extent. Hence, reduced class I MHC expression did not enable LMD cells to evade CTL recognition. It is possible that differential responses to CTL cytolysis are related to the function of perforin. Studies on CTLs, which are protected from their lytic components, indicate that there are mechanisms for inhibiting the activities of perforin (27). There was no correlation between perforin binding and susceptibility to lysis, but there were structural differences in perforin bound to resistant versus susceptible cell lines (27). These results provide indirect evidence for the presence of a perforin-inhibitory protein that permits perforin binding but prevents functional pore formation. However, our data indicated that LMD cells had DNA fragmentation after incubation with CTLs, suggesting that there was perforin pore formation and transmission of granzymes to the cancer cells. The role of perforin in resisting CTL cytolysis can be clarified in further studies using purified or recombinant perforin to examine perforin membrane binding, insertion, and pore formation. Alternatively, the resistant phenotype may be attributable to the function of an intracellular suppressor factor(s) that regulates the cell death signals initiated by CTLs through the granzyme pathway. Signaling pathways leading to apoptotic cell death and cell lysis induced by CTLs are transduced through both caspase-dependent and caspase-independent pathways (28–30). It is proposed that granzymes released from CTLs cause nuclear damage such as DNA fragmentation and chromatin condensation through a caspase-dependent pathway, whereas cytoplasmic apoptotic damage such as prelytic phosphatidylserine externalization, mitochondrial potential loss, and target cell lysis are induced by granzymes via a caspase-independent pathway (29). It is possible that suppressor factor(s) in LMD cells may inhibit signaling in this caspase-independent cytoplasmic cell death pathway. Obviously, it is of interest to determine the molecular basis of dominant resistance to cell lysis but not nuclear damage induced by CTLs in metastatic cancer cells.

The underlying premise of tumor immunology is that the immune system is capable of recognizing cancer cells and that immune recognition can lead to rejection of tumors by the host (31). Recent molecular identification of tumor antigens that are recognized by T cells further bolster the prospect of cancer immunotherapy (32, 33). However, malignant transformation is often associated with genetic alterations, providing tumor cells with mechanisms for escape from immune surveillance. Overcoming these immune escape phenotypes is crucial for successful application of cancer immunotherapy. There is increasing evidence to suggest that a large proportion of human cancers escape CTL-mediated immune surveillance by selectively down-regulating the expression of MHC class I molecules (14–16), and strategies to overcome this escape phenotype by enhancing MHC class I expression in vivo are being evaluated (34). Nevertheless, results reported in this study indicate that metastatic cancer cells acquire, during tumor progression, an additional mechanism to evade cellular destruction by CTLs. Although class I MHC expression is restored on tumor cells, metastatic cancer cells remain resistant to CTL-induced cell lysis. Therefore, immune responses induced by immunotherapy may eliminate a majority of primary cancer cells, but a population of metastatic cancer cells could remain resistant to the immune attack. These results indicate that additional intervention strategies are required for the eradication of metastatic cancer cells. Further characterization of this cytolysis-resistant trait in metastatic prostate cancer cells would give us clues in the development of strategies that bypass the blockage in apoptotic cell death and sensitize metastatic tumor cells to anticancer therapy.

REFERENCES

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