Cross-Presentation of Tumor Antigens to Effector T Cells Is Sufficient to Mediate Effective Immunotherapy of Established Intracranial Tumors

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Cross-Presentation of Tumor Antigens to Effector T Cells Is Sufficient to Mediate Effective Immunotherapy of Established Intracranial Tumors

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The systemic adoptive transfer of tumor-sensitized T cells, activated ex vivo, can eliminate established intracranial tumors. Regression of MHC class II negative MCA 205 fibrosarcomas occurs optimally following adoptive transfer of both CD4 and CD8 tumor-sensitized T cells, indicating an important function for tumor-infiltrating APC. Here, we demonstrate that during an effector response, indirect presentation of tumor Ags to transferred T cells is sufficient to mediate intracranial tumor regression. BALB/c → CB6F1 (H-2<sup>b</sup>/<sup>b</sup>) bone marrow chimeras were challenged with the MCA 205 fibrosarcoma (H-2<sup>b</sup>). The tumor grew progressively in the H-2<sup>b</sup>-tolerant chimeras and stimulated an immune response in tumor-draining lymph nodes. Tumor-sensitized lymph node T cells were activated ex vivo with anti-CD3 and IL-2, then adoptively transferred to sublethally irradiated BALB/c or C57BL/6 recipients bearing established intracranial MCA 205 tumors. The transferred T cells eradicated MCA 205 tumors in BALB/c recipients and demonstrated tumor specificity, but had no therapeutic efficacy in the C57BL/6 recipients. These data establish that tumor-associated host cell constituents provide sufficient Ag presentation to drive effector T cell function in the complete absence of direct tumor recognition. This effector mechanism has an evident capacity to remain operative in circumstances of immune escape, where the tumor does not express the relevant MHC molecules, and may have importance even at times when direct CTL recognition also remains operative. The Journal of Immunology, 2000, 165: 3656–3662.

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4 Abbreviations used in this paper: LN, lymph node; i.e., intracranial; WBL, whole body irradiation; CFDA, 5-(and-6)-carboxyfluorescein diacetate; KO, knockout; CM, complete medium.

5 Peng, L. D. E. Weng, G. E. Plautz, S. Shu, and P. A. Cohen. 2000. Helper-independent, L-selectin<sup>low</sup> CD8<sup>+</sup> T cells with broad anti-tumor efficacy are naturally sensitized during tumor progression. Submitted for publication.
Activating LN T cells
BALB/c → CB6F1 bone marrow chimeras were inoculated s.c. with 1.5 × 10^6 MCA 205 H12 tumor cells in the lower flank region bilaterally. Nine days later, tumor-draining inguinal LNs were removed under sterile conditions and single cell suspensions were prepared mechanically. Tumor-draining LN cells were prepared similarly from IFN-γ KO mice except that LNs were harvested 12 days after tumor inoculation. Cells were resuspended in CM and were activated with immobilized anti-CD3 mAb (145-2C11) in 24-well tissue culture plates at 4 × 10^6 cells/well in 2 ml CM in 5% CO_2, at 37°C for 2 days. After anti-CD3 activation, cells were harvested and further cultured in CM with 24 IU/ml of human recombinant IL-2 at 2 × 10^6/ml in gas-permeable culture bags (Baxter Healthcare, Deerfield, IL) for 3 days. Cells were harvested, washed, and resuspended in HBSS for adoptive transfer.

Adoptive immunotherapy
For recipients of IFN-γ KO effector cells, B6 or IFN-γ KO mice were injected i.c. with 1 × 10^7 MCA 205 H12 cells in 0.1 ml HBSS. Three days later, mice were treated with 5 Gy WBI from a 137Cs source then injected i.v. with 15 × 10^6 effector cells suspended in 1 ml HBSS. For recipients of BALB/c → CB6F1 bone marrow chimera effector cells, B6 or BALB/c mice were conditioned with 5 Gy WBI from a 137Cs source. Two days later, they were injected i.c. with 1 × 10^7 MCA 205 H12 or 1 × 10^6 MCA 205 G11 tumor cells in 0.01 ml HBSS. Three days later, mice were treated with 5 Gy cranial irradiation with body shielding from a 137Cs source then injected i.v. with 25 × 10^6 effector cells suspended in 1 ml HBSS.

In vivo survival of transferred cells
Effector T cells were labeled with 5-(and-6)-carboxyfluorescein diacetate (CFDA) succinimidyl ester (Molecular Probes, Eugene, OR) as previously described (16). Briefly, cultured effector cells were washed twice with HBSS, and 1 × 10^5 cells/ml were inoculated into HBSS for 15 min at 37°C. Labeling was stopped by adding cold HBSS, and cells were washed twice with HBSS before adoptive transfer. C57BL/6 or BALB/c mice were conditioned with 5 Gy WBI from a 137Cs source then were inoculated 2 days later with 1 × 10^6 MCA 205 H12 tumor cells. Three days later, mice were treated with 5 Gy cranial irradiation with body shielding from a 137Cs source then injected i.v. with 25 × 10^6 fluorochrome-labeled effector cells. Mice were sacrificed 24 h, 48 h, and 7 days after adoptive transfer. Spleens were removed, mechanically disrupted, and treated with ammonium chloride to remove RBCs. Mononuclear cells were counted with a hemocytometer and an aliquot was analyzed by flow cytometry.

Results
MCA 205 H12 fails to express detectable MHC class II molecules
To determine the potential of the MCA 205 H12 tumor to present Ags through MHC molecules, it was cultured in the presence of murine IFN-γ. As shown in Fig. 1A, MCA 205 H12 expressed high basal levels of H-2Kb, and this expression was up-regulated by 100 U/ml IFN-γ. MCA 205 H12 tumor cells are directly recognized by CD8+ T cells derived from tumor-draining LN demonstrating that this tumor is fully functional for Ag presentation. In contrast, MCA 205 H12 did not express I-A^b-, nor was it induced by treatment with 10,000 U/ml IFN-γ (Fig. 1B). A single cell suspension prepared from in vivo MCA 205 H12 tumor expressed H-2Kb and H-2Dd (Fig. 1, D and E). As demonstrated in Fig. 1F, the tumor consisted of two populations of cells, tumor cells that were I-A^b negative and CD11b negative, and ~19% CD11b- I-A^b+ host accessory cells. Previous studies from our laboratory confirmed that the CD11b+ cells had phenotypic and functional characteristics of macrophages (27). Consistent with the lack of tumor cell MHC class II expression, CD4+ LN T cells were only stimulated to secrete IFN-γ specifically by an MCA 205 tumor digest that contains the I-A^b+ cells but not by MCA 205 H12 cells alone (22). Although aberrant expression of alloimmune H-2 molecules has been described for some highly immunogenic UV-induced tumors (28, 29), we detected neither expression of H-2Kb nor H-2Dd in vivo (Fig. 1, D and E), nor that of I-A^d (not shown). Thus, MCA 205 H12 would not be expected to have the capacity to directly present Ags to I-A^d-restricted T cells or, likewise, to H-2^d-restricted T cells.

Materials and Methods
Animals
CB6F1 (H-2^rd), BALB/c, and B6(C57BL/6) mice at 6–8 wk of age were purchased from the Biologic Testing Branch, Frederick Cancer Center Research and Development Center, National Cancer Institute (Frederick, MD). B6 background IFN-γ knockout (KO) (C57BL/6-IFNGtm1Ts) mice were purchased from The Jackson Laboratory (Bar Harbor, ME). They were maintained in a specific pathogen-free environment and fed ad libitum according to National Institutes of Health guidelines.

Tumors
MCA 205 H12 was derived from the 3-methylcholanthrene-induced fibrosarcoma MCA 205 by limiting dilution cloning. MCA 207 G11 was similarly derived from MCA 207 by limiting dilution cloning. MCA 205 H12 and MCA 207 G11 were maintained by serial passage in vitro in complete medium (CM); RPMI 1640 supplemented with 10% heat-inactivated FCS, 0.1 mM nonessential amino acids, 1 mM sodium pyruvate, 2 mM l-glutamine, 100 μg/ml streptomycin, 100 U/ml penicillin, 50 μg/ml amphotericin B (all obtained from Life Technologies, Grand Island, NY), and 5 × 10^{-5} M 2-ME (Sigma, St. Louis, MO).

Flow cytometry
In vitro cultured tumor cells were treated with the indicated concentration of murine IFN-γ for 24 h and harvested from culture by trypsin/EDTA treatment. Single cell suspensions were prepared from in vivo tumors by digestion in 0.1% collagenase type IV, 0.01% DNase I, and 2.5 U/ml hyaluronidase type V (Sigma) for 3 h at room temperature as previously described (13). Tumor-draining LNs were mechanically prepared as a single cell suspension. All cells were incubated with Fc Block (PharMingen, San Diego, CA) for 30 min on ice, then stained with the indicated fluorochrome-conjugated Abs; anti-H-2^b, anti-H-2^d, anti-I-A^b, anti-I-A^d, anti-CD62L, anti-CD4, anti-CD8, anti-CD11b, or isotype control rat IgG2, or mouse IgG2a (all obtained from PharMingen) at 4°C for 30 min. Stained cells, 10^6, were analyzed by flow cytometry using the CellQuest software package (Becton Dickinson, San Jose, CA).

Bone marrow transplantation
CB6 mice were treated with a single fraction of 10 Gy whole body irradiation (WBI) from a 137Cs source. Bone marrow obtained from BALB/c mice was injected i.v. into recipients 24 h after WBI. Mice received ciprofloxacin 100 μg i.p. once a day for 20 days posttransplant. BALB/c → CB6F1 bone marrow chimera was used to generate tumor-draining LN cells between 4 and 5 mo posttransplant.

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Regression of i.c. MCA 205 tumors occurs in the absence of IFN-γ

Regardless of the observed expression of MHC on tumor cells in vitro, it was conceivable that modulation of tumor MHC expression could occur during the height of the effector response in vivo, through paracrine effects of soluble mediators, such as IFN-γ, released by T cells or host cells. MCA 205 H12 tumor-draining LNs were obtained from IFN-γ KO or normal B6 mice and were transferred to IFN-γ KO or normal B6 mice bearing established i.c. MCA 205 H12 tumors. All tumor-bearing mice were cured whether or not the effector T cells produced IFN-γ (Fig. 2). T cells from IFN-γ-deficient mice were also effective in IFN-γ KO hosts (p = 0.0006 compared with untreated mice). Although late tumor recurrence occurred in two IFN-γ KO mice treated with IFN-γ KO T cells, the difference did not reach statistical significance (p = 0.43). An attenuating effect of host IFN-γ production on tumor progression was also manifested in normal mice not treated with T cell transfer compared with IFN-γ KO recipients (27 vs 21 days median survival, respectively; p = 0.003). Nevertheless, IFN-γ production was not an essential component of the antitumor response mediated by the transferred effector T cells.

MCA 205 H12 stimulates tumor-draining LN in H-2d chimeric mice

CB6 mice (H-2^bd) were transplanted with bone marrow from BALB/c mice following myeloablative WBI. The BALB/c → CB6F1 bone marrow chimeras were allowed to reconstitute their T cell repertoire for 4 mo following the transplant. T cells in such mice were tolerant of H-2^b-expressing tissues but were primed in secondary lymphoid tissues by APC derived from the H-2^d donor hematopoietic system. MCA 205 H12 tumors grew progressively, expressed H-2K^b in the chimeric hosts, and contained a significant population (40%) of CD11b^+ I-A^d cells but no I-A^b cells (Fig. 3, C and D). Moreover, the tumor stimulated hyperplasia in draining LN...
E-2d-restricted effector T cells derived from the bone marrow chimera transfer of 25\(^{3}10^5\) irradiated B6 mice in the absence of effector T cell transfer consistent with a nonirradiated recipients and was equally lethal in BALB/c and B6 recipients. The tumor grew progressively in the irradiation of an established i.c. tumor is not essential but does augment the efficacy of the transferred T cells (24). The tumor progressed in BALB/c recipients with i.c. MCA 205 H12 cells (data not shown). The established tumors were subsequently treated with local cranial irradiation (5 Gy) followed by adoptive transfer of activated effector T cells. We have previously demonstrated that local irradiation was necessary to permit growth of the allogeneic tumor because the MCA 205 H12 clone has been main-

Activated LN cells mediate regression of i.c. tumors

BALB/c and B6 mice were treated with sublethal WBI, and, 2 days later, MCA 205 H12 was inoculated i.c. The sublethal WBI before tumor inoculation was necessary to permit growth of the allogeneic tumor because nonirradiated BALB/c recipients were competent to reject 10\(^3\) i.c. MCA 205 H12 cells (data not shown). The established tumors were subsequently treated with local cranial irradiation (5 Gy) followed by adoptive transfer of activated effector T cells. We have previously demonstrated that local irradiation of an established i.c. tumor is not essential but does augment the efficacy of the transferred T cells (24). The tumor grew progressively in the irradiated recipients and was equally lethal in BALB/c and B6 recipients (Fig. 4). The survival time in irradiated BALB/c mice was similar to irradiated B6 mice in the absence of effector T cell transfer consistent with a subtherapeutic remnant alloreactive T cell or NK activity. The adoptive transfer of 25 \times 10^5 activated LN T cells was able to cure an established tumor in the BALB/c recipients but had no apparent therapeutic effect in the B6 recipients. Fig. 4, a compilation of three independent experiments of identical design, showed a highly significant survival difference for the treated BALB/c mice compared with each other and the controls (p < 0.0001). In contrast, there was no survival difference for B6 mice treated with effector cells compared with untreated B6 mice (p = 0.35). Likewise, treatment of B6 mice with a higher dose of effector cells (5 \times 10^5) did not extend survival compared with untreated controls (data not shown). The B6 mice all died from tumor progression as evidenced by swelling of the skull and development of neurological dysfunction. Tumor progression as the cause of death was confirmed by necropsy in sentinel B6 mice treated with adoptive transfer (not shown).

Specific tumor Ags are presented by APC

The MCA 205 tumor typically contains a significant population of infiltrating macrophages. In BALB/c mice bearing i.c. MCA 205 H12 tumors, the expression of H-2d molecules was observed on the CD11b\(^{+}\) macrophages, whereas the CD11b\(^{-}\) tumor cells expressed H-2d (Fig. 5). Thus, H-2\(^{d}\)-restricted effector T cells derived from the bone marrow chimeras were only presented with cognate Ags through the tumor-infiltrating normal host cell constituents and not by the tumor cells. A direct response of T cells from the chimeras to the H-2\(^{d}\) tumor cells was not apparent in vivo in the B6 mice. Moreover, in vitro coculture of MCA 205 H12 tumor cells with effector T cells did not elicit any IFN-\(\gamma\)-secretion (data not shown). To confirm that the tumor regression observed was Ag-specific rather than mediated by an atypical allo-Ag response, MCA 205 H12-sensitized T cells were transferred to BALB/c recipients bearing i.c. MCA 207 G11 tumors. MCA 207 G11 is a subclone of the MCA 207 fibrosarcoma (H-2\(^b\)). In previous experiments using syngeneic B6 mice, we have demonstrated that MCA 207 Ags were not recognized by MCA 205-sensitized LN cells (13). As demonstrated in Fig. 6, the transferred effector T cells did not extend survival of mice bearing MCA 207 G11 tumors compared with untreated mice (p = 0.9). In contrast, mice bearing MCA 205 H12 tumors treated with transferred had significantly prolonged survival compared with untreated mice (p = 0.0017).

Transferred effector T cells survive equally well in BALB/c and B6 recipients

We have used CFDA-labeled effector T cells to study the trafficking and persistence of the transferred cells in tumor-bearing hosts (16, 17). CFDA labeling does not affect the antitumor effector function of the transferred T cells and permits their identification for at least 1 wk following adoptive transfer. Spleens were removed from irradiated tumor-bearing BALB/c or B6 mice following the adoptive transfer of 25 \times 10^5 CFDA-labeled effector T cells. Table I documents the similar survival of transferred T cells in the BALB/c or B6 recipients up to 7 days after adoptive transfer. Fig. 7 demonstrates that similar percentages of CD4 and CD8 T cells were recovered from the BALB/c and B6 recipients 48 h after transfer. Thus, the failure of the MCA 205 H12-sensitized chimeric T cells to function in the B6 recipients was not caused by their rapid elimination.
Discussion

There are likely multiple effector mechanisms through which T cells can orchestrate tumor eradication. Direct cytotoxicity by CD8+ T cells has been amply documented in many tumor immunotherapy models and has an intrinsic theoretical appeal because most tumors arise from somatic tissues that express only MHC class I molecules. In addition, knockout studies have demonstrated the involvement of T cell perforin expression in several models of tumor rejection (30-34). However, direct cytotoxicity is not the only effector mechanism and was certainly not necessary in this experimental model. Despite an inability of effector T cells to directly interact with tumor cells in a relevant MHC context, sufficient mechanisms remained to mediate tumor rejection. One particular advantage of using adoptive transfer of effector T cells into sublethally irradiated tumor-bearing hosts was that it permitted us to investigate indirect Ag presentation during the sensitization phase separately and distinctly from the effector phase. Moreover, this tumor model measured a biologically relevant mechanism rather than an in vitro surrogate marker.

In this experimental model, cross-priming of T cells by bone marrow-derived APC was the predominant mechanism of sensitization to naturally occurring tumor Ags. It has been previously documented that, during the afferent phase of the immune response, Ags expressed in the periphery are acquired by APC and presented in LNs in a MHC-restricted fashion to prime both naive CD4 and CD8 T cells (35, 36). Similarly, sensitization of T cells to foreign model tumor Ag was demonstrated to occur through cross-priming (37). In the BALB/c → CB6F1 bone marrow chimera, cross-priming to natural tumor Ags was mediated by APC of the hemopoietic lineage thus restricted by H-2d molecules. Importantly, the existence of cross-priming through H-2d does not necessarily exclude the possibility of direct sensitization of H-2b-restricted CD8+ T cells by tumor cells. In the BALB/c → CB6F1 bone marrow chimera, thymic selection occurs in the presence of radio-resistant epithelium expressing H-2d molecules, and naive T cells restricted by H-2d are generated (38-40). Thus, the opportunity for naive T cells with H-2d specificity to become sensitized in tumor-draining LN and become activated ex vivo through Ag-independent anti-CD3 stimulation is available. Such H-2d-restricted effector T cells would be equally tumoricidal through their direct interactions with tumor in either the B6 or BALB/c recipients. Therefore, the absence of any therapeutic efficacy in B6 mice, even at supertherapeutic cell doses, strongly argues that direct tumor priming of T cells is inconsequential in this tumor model as it has been found in others (41). MCA 205 H12 does not metastasize to draining LN, even at very advanced stages of growth so is unlikely to be present at the site of Ag presentation to naive T cells. Furthermore, the MCA 205 H12 tumor cells do not express costimulatory molecules or MHC class II molecules that are typically required in model systems where direct sensitization is evident (42, 43).

Cross-priming illustrates that the immune system uses specialized APC to communicate the presence of Ag and danger signals in the periphery to the protected environment of the LN, where the cellular architecture is optimized to generate an appropriate response by naive T cells. However, as immature DC acquire Ag in the periphery, the milieu can affect their differentiation (44). For example, the presence of TGF-β expressed by many tumors during Ag acquisition causes APC to generate a deviant T cell response to a foreign Ag and loss of a delayed-type hypersensitivity reactivity (45). Thus, it is not predetermined that tumor Ag acquisition by DC will necessarily generate the type of T cell response that leads to tumor regression. Moreover, the nature of the Ags, their quantity, and presence of cognate CD4 responses during sensitization determine the outcome of cross-priming and can lead to either tolerization or augmentation of CD8 responses (46-49). The mode

<table>
<thead>
<tr>
<th>Time Posttransfer</th>
<th>Mouse No.</th>
<th>Cell Yield</th>
<th>CFDA + (%)</th>
<th>No. CFDA +</th>
</tr>
</thead>
<tbody>
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<td>24 h</td>
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<td>2.6 × 10^6</td>
<td>32.6</td>
<td>0.9 × 10^6</td>
</tr>
<tr>
<td>24 h</td>
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<td>26.8</td>
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<td>B6 2</td>
<td>5.5 × 10^6</td>
<td>31.4</td>
<td>1.7 × 10^6</td>
</tr>
<tr>
<td>48 h</td>
<td>B6 3</td>
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<td>31.2</td>
<td>1.1 × 10^6</td>
</tr>
<tr>
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<tr>
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<tr>
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</tr>
<tr>
<td>7 days</td>
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<td>4.4</td>
<td>0.7 × 10^6</td>
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<tr>
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<td>19.8</td>
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<td>18.9</td>
<td>0.7 × 10^6</td>
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*Activated tumor-draining LN cells from CB6F1 chimeric mice were labeled with CFDA and 25 × 10^6 cells were transferred i.v. to hosts bearing 3-day i.c. MCA 205 H12 tumors. All mice were treated with 5 Gy WBI 5 days before transfer of effector T cells. spleens were removed at the indicated time after transfer and treated with ammonium chloride to remove RBC. Percentage CFDA + cells was determined by FACS.
of Ag presentation is likely to have great importance for priming T cell responses to progressive naturally occurring tumor Ags where aberrantly expressed or mutated proteins are contained within a predominantly normal array of self Ags. There is evidently some plasticity in the differentiation potential of tumor-sensitized T cells that can be manipulated by the conditions of ex vivo activation. The sensitized T cells in the tumor-draining LN do not promote progressive tumor growth nor do they mediate tumor regression upon immediate adoptive transfer. However, sensitized LN T cells acquired potent Ag-specific reactivity following ex vivo activation, indicating that a critical differentiation step or functional change had occurred. This conveniently permitted us to determine the requirements for Ag presentation solely during the effector phase through adoptive transfer to secondary hosts.

The salient finding of this study is that tumor-infiltrating APC play an important role in the effector phase of the antitumor immune response and are sufficient to coordinate tumor regression with Ag-specific T cells in the absence of direct tumor recognition. DC are one differentiated form of hemopoietic precursors that are optimized to acquire Ag and stimulate naive T cells. Macrophages have some overlapping lineage and phenotypic characteristics with DC but perform distinct functions in peripheral tissues. Through their ability to acquire and process Ag, either macrophages or DC would have the capacity to convey the local presence of tumor Ag to effector T cells even when the T cells do not directly recognize tumor cells or do so poorly (50–52). This reactivation is likely critical for tumor-infiltrating CD4+ T cells and also for CD8+ T cells when the tumor has lost expression of the relevant MHC molecules (26). In addition, these experiments provoke an interesting question of whether the tumor-infiltrating APC might provide a more effective stimulus for CD8+ effector T cells than the tumor cells under most circumstances. We have previously demonstrated that infiltration of tumor by adoptively transferred T cells and costimulation of T cells through LFA-1 are both required for effector function (17, 53). Reactivation of adoptively transferred T cells in situ might be more efficiently provided by APC that typically express higher levels of LFA-1 ligands such as ICAM-1 and ICAM-2 than tumor cells. Although the current experiments were designed to only address whether indirect Ag presentation to effector T cells was sufficient, future experiments could potentially test the relative effectiveness of APC vs tumor cells for reactivation.

An important function of APC stimulation of effector CD4+ and CD8+ T cells could be the induction of cytokines with paracrine effects. Our previous studies demonstrated the necessity of CD4+ T cell participation in the adoptive immunotherapy of i.c. or s.c. MCA 205 tumor (13, 15). Likewise, CD4+ T cell-dependent effector mechanisms have also been demonstrated in a vaccination-challenge model (54). Interestingly, CD4+ CD62Llow T cells isolated from tumor-draining LN can cure a tumor that does not express detectable levels of MHC class II, following in vitro and in vivo depletion of CD8+ T cells. This observation encouraged us to re-examine the concept of “helper function” in this tumor model system. Rather than merely serving as a source of IL-2 for cytotoxic CD8+ T cells, apparently the CD4+ T cells mediated an antitumor response through paracrine effects of additional secreted cytokines (55). Although IFN-γ is an important cytokine with paracrine function, our experiments demonstrated that IFN-γ-decient T cells could nevertheless cure tumors in IFN-γ-deficient hosts. Thus, there are sufficient redundant effector mechanisms mediated through additional cytokines.

The tumor-infiltrating APC could also contribute a critical effector function beyond Ag presentation to T cells. The large majority of the APC that infiltrate the MCA 205 tumors have phenotypic and functional characteristics of macrophages. Activated macrophages can secrete inflammatory cytokines and reactive substances such as NO with paracrine effects as well as perform phagocytosis. Their distribution throughout the tumor would permit localized display of acquired tumor Ags to specific T cells. The specificity provided by the T cells could anatomically localize activation of nonspecific cytolytic function by macrophages to limit collateral damage to adjacent normal structures. Such an anatomically localized mechanism of tissue destruction has obvious importance in delicate structures such as the CNS.

Generation of effector T cells restricted by the APC of the tumor-bearing host but unable to interact directly with the tumor provides independent experimental confirmation that dominant indirect presentation of tumor Ags can occur, not only during initial T cell sensitization, but also during the effector phase of tumor rejection. The indirect mechanism of tumor eradication described here does not preclude other mechanisms, such as direct cytotoxicity, from being predominant under conditions where direct interactions of effector T cells with the tumor is permitted. Nonetheless, the critical clinical importance of T cell effector mechanisms that remain operative in the face of tumor escape through modulation of MHC expression is already apparent (4, 5, 8, 26, 56). This report confirms the ability of adequately implemented T cell adoptive therapy fully to withstand such escape modulations. It also hints at the potential use of augmenting APC numbers and function at the effector phase through systemic delivery of cytokines in conjunction with adoptive transfer of suitably primed and activated T cells.

References


