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Regulation of the Immune Response to Antigens on the Malignant Cell Surface*

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Introduction

The ability of mammalian species to mount immune responses against structures present on the cell surface was discovered by Landsteiner [46] in studies of blood group antigens. The work of Gorer [20], clearly showed that tumor grafts would grow in syngeneic animals, but were rejected in allogeneic strains of mice; this then led to the study of the immunologic basis of graft rejection phenomena and eventually to successful organ transplantation [5]. It has been recently shown that primary tissue grafts from histoincompatible donors are consistently rejected by cellular immune responses of the recipient. The cells responsible for graft rejection belong to the $Lyt1^+2^-$ subset of thymus-derived (T) cells [48]. The principal antigens which are recognized in the process of graft rejection are those encoded by genes in the major histocompatibility complex of the species [10], such as the H-2 locus in the mouse and the HLA locus in man.

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Abbreviations used in this paper: ABA p-Azobenzenearsonate; *ADCC* Antibody-dependent cell-mediated cytotoxicity cell; *APC* Antigen-presenting cell; *cDNA* Complementary DNA sequence; *CRI* Cross-reactive idiotype; *CTL* Cytolytic thymus-derived lymphocyte; *HLA* Human leukocyte antigen gene complex; *IV* Intravenous; *KLH* Keyhole limpet hemocyanin; *mRNA* Messenger ribonucleic acid; *NK* Natural killer cell; *NP* 4-Hydroxy-3-nitrophenyl acetyl; *T* Thymus derived; *Ts* Suppressor T cell; *Ts1* First order suppressor T cell; *Ts2* Second order to suppressor T cell; *Ts3* Third order suppressor T cell; *TsF1* First order suppressor T cell factor, produced by Ts1; *TsF2* Second order suppressor T cell factor, produced by Ts2; *UV* Ultraviolet; V_H Heavy chain variable region; V_L Light chain variable region

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The fact that tumors bear antigens which the syngeneic host is capable of recognizing and directing an anti-tumor immune response against was first discovered by Foley [16], and then extended by several other groups [42, 58, 67]. The biochemical characterization of such tumor antigens is reviewed elsewhere in this volume, and will not be discussed here. It is our intention to summarize and review studies which have focused on the nature of the immune response against tumor antigens as well as the mechanisms by which the anti-tumor immune response is regulated. Since the immune response stimulated by hapten-coupled spleen cells is in many ways similar to the response against syngeneic tumor antigens, we will indicate where studies of anti-hapten immunity have extended our knowledge of the regulation of immune responses. However, this report will primarily focus on what is specifically known about anti-tumor immune responses; several reviews of the regulation of immune responses against haptenic determinants have been published recently [31, 57]. Finally we will discuss recent studies which have indicated that the anti-tumor immune response is directed, at least in part, against determinants that are related to the specific gene(s) which are responsible for transformation.

The Role of Suppressor T Cells in Regulating Anti-tumor Immune Responses

The work of the Hellstroms [33, 34] indicated that tumor-bearing animals are unable to mount an effective immune response against their syngeneic tumors and this inhibitory effect could be adoptively transferred by sera from tumor-bearing animals. Moreover, the sera could also block in vitro cell-mediated cytotoxicity directed against tumor cells [32]. Because the serum factor appeared to react with anti-immunoglobulin antisera, it was initially believed that immunoglobulins in the sera of tumor-bearing animals were able to abrogate the anti-tumor immune response; these antibodies were termed blocking antibodies.

Fujimoto et al. [18] demonstrated that the anti-tumor immune response could be suppressed by the transfer of thymus or spleen cells and not by serum obtained from tumor-bearing syngeneic mice. It was shown that these cells were Thy 1.2 positive, and could be eliminated by treatment with anti I-J alloantisera and complement [65]. Thus these cells, which could specifically inhibit immune responses to syngeneic tumor, were considered subsets of suppressor T cells (Ts). Other physical and functional characteristics of Ts active in tumor immunity were ascertained and are shown in Table 1. The Ts arise shortly (24–48 hours) after tumor implantation and remain for three days after tumor removal. The cells have a low density and can be readily isolated by centrifugation on discontinuous Ficol gradients.

That more than one suppressor cell is involved in suppressing anti-tumor immune responses was shown by the following set of experiments. The suppressor cells found within the thymus seven days after primary tumor challenge were found to secrete a soluble suppressor molecule (TsF). The TsF, when administered to immune mice led to the abrogation of their capacity to respond to a tumor challenge [24]. Immunochemical characterization revealed the molecule to be a protein of 33 000–68 000 daltons, sensitive to pronase, resistant to RNAse, and labile to both

Table 1. Characteristics of tumor antigen specific suppressor cells

Cell surface phenotype
I-J$^+$
Thy 1$^+$
TSF$^+$
Ly 1$^+$2$^-$ (Ts1)
Ly1$^+$2$^+$ (Ts2)
Physiology of Ts1
Activated by soluble tumor antigens
Appear within 24 h of tumor inoculation
Disappear within 72 h after tumor removal
Found in lymph node, spleen, and thymus of tumor-bearing mice
Cyclophosphamide sensitive
Inhibit generation of effector T cells in vivo and in vitro
Elaborate an I-J$^+$ antigen specific factor (TsF)
Physiology of Ts2
Activated by TsF
Inhibits effector T cell function, possibly by activating a third order supressor (Ts3)

temperatures of 56 °C (for more than 1 hour) and low pH (2.4). These latter characteristics suggest that a particular tertiary conformation is required for tumor suppressor factor function. The antigen-binding specificity of TsF was determined by the ability to selectively absorb the functional activity on homologous but not heterologous tumor cells. Not only were such molecules antigen specific, but they were also found to contain determinants encoded by the I-J subregion of the H-2 complex located on chromosome XVII [60].

Thus TsF contains both antigen binding and major histocompatibility encoded determinants. It is possible to generate specific antibodies against this TsF molecule [24]. The antibody can neutralize Ts cells, which apparently express the TsF molecule on the cell surface. We have shown that TsF seems to be able to stimulate the development of another set of Ts in naive mice, in the absence of tumor [60]. We termed the Ts subset induced by tumor antigen in the primary tumor-bearing host first order or Ts1 suppressors. The subset of Ts induced by TsF in naive recipients were termed second order or Ts2 suppressors. The obscure nature of the tumor antigen prevented a detailed analysis of structural elements on TsF relevant to antigen-specific binding and Ts2 activation, so we turned to other systems to analyze TsF structures immunochemically.

The interaction of suppressor T cell subsets has been studied in great detail in a variety of haptenic systems. It is possible to induce hapten-specific Ts1 cells by intravenous (IV) administration of hapten-coupled spleen cells [1, 27, 90]. In the azobenzenearsonate (ABA) haptenic system, it has been shown that in A/J mice immunized with ABA-KLH the majority of anti-ABA antibodies express a phenotypic structural marker known as cross-reactive idiotype (CRI) [45]. The CRI is actually a composite of structures, including those produced by interaction determinants of both heavy and light chain variable regions. The CRI family includes structures associated with the antigen-combining site and those not directly involved in antigen binding. Studies of a first order Ts1 cell in the ABA

system have revealed idiotype-like molecules on the cell surface, as detected by a rabbit anti-idiotype antibody [28]. A TsF molecule produced by such Ts1 (called TsF1) was found to have CRI structures encoded by V_H genes, but not V_L genes [81]. The idiotype-like structure was not, however, the same idiotype-like structure associated with the anti-ABA immunoglobulin antigen combining site. It appears that the idiotypic region of TsF is related to the non-antigen binding idiotypic region of anti-ABA immunoglobulin. Furthermore I-J molecules were also apparent on the TsF1. The TsF1 was found capable of inducing a second set of Ts, Ts2, which in this system had complementary anti-idiotypic receptors for the idiotype-like determinant on the TsF1 [82]. Thus the Ts1 and Ts2 subsets interact through idiotype-related structures.

Additional studies of ABA-specific suppressor T cells have revealed a third order population of suppressor T cells, Ts3 [83], which are initially activated by ligand and triggered by a factor (TsF2) produced by the Ts2 cell. This same general pattern of Ts1 producing TsF1, TsF1 activating Ts2, and Ts2 producing TsF2 which activates Ts3 has been observed (with some differences) in the NP system [51]. In all cases the Ts3 requires antigen priming in addition to TsF2 in order to suppress anti-hapten immune responses [80]. Recent work from our laboratory also indicates the anti-tumor suppressor pathway probably contains a third order Ts3-like cell, which can be activated by TsF2 administered to primed animals (S. Schatten and M. Greene, unpublished data).

The suppressor pathway activated by growing tumors appears to be analogous to the pathway activated by the IV administration of hapten coupled spleen cells. Since tumors are known to shed antigen into the circulation [65], it was of interest to explore whether IV administration of antigenic membrane fragments could activate the tumor suppressor T cell cascade. As shown in Table 2, the administration of tumor cell membranes IV results in the appearance of splenic Ts capable of markedly suppressing the immune response against tumor antigens upon adoptive transfer into the immunized host [65]. We have also found that IV administration of polyoma tumor membranes results in a markedly reduced primary response against a highly antigenic polyoma virus transformed cell line (J. Drebin and M. Greene, unpublished data). It appears that tumors may activate the suppressor T cell pathway, at least in part, by continuously shedding cell surface

Table 2.

Priming	Transfer	Challenge	Footpad swelling (10^{-2} mm$^2 \pm$ SE)
S1509a	–	S1509a	31.8 ± 3.8
YAC	–	S1509a	16.6 ± 2.0
S1509a	5×10^7 TS IV	S1509a	14.2 ± 1.3*
S1509a	5×10^7 m.p.s IV[a]	S1509a	16.3 ± 1.5*
–	–	S1509a	14.3 ± 1.3*

* $p < 0.005$

[a] m.p.s. = membrane-primed splenocytes: spleen cells from naive mice given IV tumor membranes

Induction of tumor-specific delayed type hypersensitivity suppressor cells by IV administration of syngeneic tumor membrane preparations to A/J mice. Adapted from Ref. 65

antigens into the circulation and bypassing ordered antigen presentation. The importance of tumor antigen presentation will be discussed further below. The generality of suppressor T cell activation by tumors growing in vivo has now been established by a number of groups for a variety of tumor types [2, 12, 50, 54].

Anti-Tumor Effector Cells

It is now clear that distinct subsets of T cells are involved in generating an effective immune response [7, 41]. Members of these different T cell subsets can be phenotypically classified by the Lyt differentiation antigens which they express on their cell surface. Both Ly 1+2− delayed type hypersensitivity effector cells and Ly 1−2+ cytolytic T cells are thought to be derived from an Ly 1+2+ precursor cell. The role of different T cell subsets in anti-tumor immune responses has not been entirely defined. Ly 1+2+ cells have previously been shown to be active in vivo [74] and in vitro [73] against syngeneic MCA-induced sarcomas. Fujimoto and associated have shown that anti-S1509a CTL can be generated in vitro. They have also demonstrated the ability of S1509a activated Ts to block an anti-S1509a cytolytic T lymphocyte (CTL) response in vitro [19]. However, the degree of killing by anti-S1509a Ly 1−2+ CTL was quite limited.

In the S1509a tumor system the Lyt 1−2+ cytolytic T cell does not appear to be discernibly involved in in vivo anti-tumor immune responses, as determined by adoptive transfer and Winn assay [4]; T cells bearing the Ly 1+2− phenotype are the predominant cell type involved in mediating immunity to S1509a in vivo. These same Lyt1+2− cells can be shown to specifically proliferate in vitro in response to S1509a tumor antigens (Table 3). Most relevant to the in vivo response is that the Lyt 1+2− subset's proliferative response can be specifically blocked by the administration of Ts, prior to assay. Thus the immune Lyt 1+ cell proliferative response appears to be the in vitro correlate of the Lyt 1+ cell-mediated in vivo anti-tumor immune response in the S1509a system. It may be that many different subsets of T cells can respond to tumor antigens, and the predominant subset

Table 3.

	Priming	Re-stimulator	Responder *cell treatment*	*cpm*
Exp. 1	S1509a	S1509a	–	16000
	YAC	S1509a	–	2000
Exp. 2	S1509a	S1509a	C' only	7000
	S1509a	S1509a	anti Thy 1.2+C'	1000
Exp. 3	S1509a	S1509a	–	15000
	S1509a	S1509a	–	7000
	+			
	5×10^7 Ts IV			

Specific proliferation of S1509a tumor immune T cells, and its adoptive suppression by Ts from tumor-bearing animals

identified may be a function of both the specific tumor and the immunologic assays employed.

Unresponsiveness

The lack of general increase in malignant disorders in nude mice [52], patients with DiGeorges syndrome, and immunosuppressed transplant recipients has led to a reformulation of the original immune surveillance hypothesis of Thomas [6]. It is clear that classical T cell-mediated surveillance is not involved in the response of mice to small tumor inocula [22], since there is no evidence of immunologic memory following rejection of these inocula (Table 4). Moreover T cell depleted mice have the same rejection frequency as normal immunocompetent hosts. It is of interest, however, that the IV administration of tumor membranes, which is known to induce Ts capable of abrogating a T cell-mediated anti-tumor immune response, seems to enhance the development of lethal tumors in mice receiving small tumor inocula. It was considered possible that Ts generated by the IV administration of antigenic membranes may block the activity of the cell population (NK, ADCC, macrophage) which is responsible for the non-adaptive immune response to tumor antigens. However, transfer of suppressor T cells into naive mice given a small tumor inocula did not affect tumor incidence. Thus it is possible that the soluble tumor membrane directly limits such natural non-adaptive anti-tumor mechanisms. If circulating tumor antigen induces phenotypic tolerance, in addition to activating suppressor T cell, strategies will have to be devised to overcome both types of unresponsiveness. A more detailed understanding of the role of shed antigen in blocking non-adoptive anti-tumor responses may be necessary in order to design rational modes of immunotherapy.

Induction of Tumor-Specific Ts by Ultraviolet (UV) Irradiation

The shedding of antigen into the circulation may be one way in which growing tumors can generate Ts. An apparently different mechanism was discovered by

Table 4.

Administered cell #	Primary tumor incidence (%)	Incidence on secondary challenge of primary challenge survivors (%)
10^2	3/20 (15)	3/14 (21)
10^3	5/20 (25)	2/10 (20)
10^4	13/20 (65)	3/6 (50)
10^2 (+1μg 3M KCl S1509a tumor extract IV)	7/10 (70)	

Nonadaptive response to a small S1509a tumor inocula and the effect of tumor-membrane administration on the primary response. Secondary challenge with 10^2 tumor cells.

Kripke and co-workers [44], and further studied by Spellman and Daynes [76]. It was observed that ultra-violet radiation (UV) induced sarcomas possess antigens which lead to their rejection in normal syngeneic mice (Table 5). If syngeneic mice are UV-irradiated prior to tumor challenge, the tumors are not rejected, and in fact can grow and kill the host. Based on findings in other tumor systems, it was not surprising to find that UV-irradiated mice with growing tumors have in their spleens a population of Ts which can suppress an anti-tumor immune response when adoptively transferred into naive recipients. However, tumor-specific Ts are present in the spleens of UV-irradiated mice prior to tumor challenge; that is UV-irradiation alone generates Ts which can enhance the growth of UV-induced tumors.

The mechanism by which UV irradiation leads to the generation of Ts has been studied. Hapten-specific Ts can be efficiently generated by priming a UV-treated animal with UV-treated hapten coupled spleen cells. Recent studies from our laboratory [29] have shown that UV irradiation results in a marked depression of I-A$^+$antigen-presenting cell (APC) function, without otherwise inhibiting the functional capacity of macrophages or lymphocytes. It is likely that the I-A$^+$ APC population circulates through the skin, since repeated UV treatment to the skin results in loss of I-A$^+$ APC function in all lymphoid tissues, as well as the skin (Perry and Greene, submitted for publication). It is the defect in antigen-presenting function that is considered to lead to Ts generation. Lyt 1+ helper or Lyt 1+ effector T cells require antigen presentation in the context of APC cell surface molecules, particularly products encoded in the I region of the H-2 complex. UV-irradiated APCs are unable to present antigen, and Ts, being less fastidious about the context in which they recognize antigen, are possibly activated instead. Alternatively, another subset of UV-resistant I-A$^-$ APC, may be capable of presenting ligand to Ts but not effector T cells. Thus UV-induced Ts and IV antigen-induced Ts are both activated by antigen that is not effectively presented by I-A$^+$ APCs. In both cases the Ts so generated are functionally Ts1-like cells with the ability to suppress the induction of immunity rather than to limit ongoing immune reactions.

The ability of UV irradiation to specifically activate Ts which enhance the growth of any syngeneic UV-induced tumor may relate to the presence of a common UV-induced tumor antigen on UV-transformed cells [17]. Both effector cell and suppressor cell reactivity can be expressed against this common antigen. It seems

Table 5.

Host	Response
Naive	Tumor rejection
Naive, UV treated	Lethal tumor growth
Immune	Tumor rejection
Immune, UV treated	Tumor rejection

UV irradiation prevents the rejection of UV-transformed cells in naive syngeneic mice, but has no effect on the response of tumor-immune mice. This indicates UV interferes with immune effector generation rather than immune effector function. Adapted from Ref. 17

reasonable that UV irradiation of the skin might rapidly lead to the expression of this antigen, prior to the occurrence of overt transformation. In the absence of APC I-A^+ function following UV irradiation this antigen would stimulate Ts. These Ts could then enhance the growth of UV-induced tumors, which also bear the antigen, following tumor cell challenge. This mechanism of generation of Ts reactive to UV tumor antigens remains an hypothesis, however.

The Effect of Anti I-A Alloantisera on Tumor Immunity

The importance of APC function in determining effector or suppressor responses to UV-induced tumors prompted us to study the role of APC function in immune responses to the chemically transformed S1509a fibrosarcoma. Since APC-T cell interactions require identity at the I-A subregion between both cell populations [71], we examined the effects of anti I-A alloantiserum on S1509a growth in immune syngeneic mice [62].

Anti I-A antisera can be prepared by immunizing mice of a particular strain with lymphoid cells from a strain differing only at the I-A subregion. Alternatively, one can immunize across K and I-A region differences, and absorb anti-K antibodies onto tumor cells which express K region products but not I region products. In vivo administration of microliter quantities of anti I-A^k antisera, prepared by the latter method, resulted in marked enhancement of tumor growth in tumor-immune mice rechallenged with live tumor cells. Moreover, spleen cells removed from mice during anti I-A treatment contain a population of Ts which can suppress an anti-tumor immune response upon adoptive transfer (Table 6). Similar studies have been conducted in the ABA hapten system [63]. The specific in vivo interaction of anti I-A antibodies with APCs was shown by immunizing [A × B]F1 mice with hapten

Table 6. Tumor size ($mm^2 \pm SE$)

Transfer	Day 3	Day 5	Day 7	Day 9
5×10^7 tumor immune spleen cells	5 ± 0.4	5 ± 0.2	9 ± 0	15 ± 2.5
5×10^7 tumor immune spleen cells anti-IA treated in vivo for 5 days prior to transfer	12 ± 0.7*	24 ± 2.0*	27 ± 2.4*	35 ± 4.5*
5×10^7 normal spleen cells	11 ± 0.8*	22 ± 1.0*	25 ± 1.6*	33 ± 4.0*

* $p < 0.005$

Anti I-A antiserum treatment results in loss of spleen cell anti-tumor reactivity upon adoptive transfer. Adapted from Ref. 62

coupled APCs of either parental type A or B. Anti I-A to parental A structures limited A strain APC activation of F1 T cells but not B strain APC activation of F1 T cells and vice versa. This indicates the critical role of I-A structures on APC and their interaction with anti I-A antibodies. These studies also clearly showed the blockade of effector cell response and enhancement of suppressor cell generation which resulted from administration of anti I-A alloantiserum in vivo.
The ability of anti I-A reagents to block antigen presentation to T effector cells and possibly activate Ts in vitro has been recently reported by Berzofsky and Richman [3]. Nepom and associates [55, 56] have also demonstrated inhibition of specific immune responses by monoclonal anti I region antibodies in vitro. Sprent and co-workers have confirmed that anti I-A alloantisera, or a mixture of anti I-A and anti-I-E monoclonal antibodies can block antigen presentation to T helper cells in vivo [77, 78]. McDevitt's group has recently shown that Ir gene restricted humoral responses and development of experimental allergic encephalitis are also suppressed by administration of monoclonal anti I-A in vivo [69, 79]. The ability of anti I-A reagents to directly block antigen presentation has been clearly demonstrated. Tumor growth is enhanced by anti I-A serotherapy or UV irradiation, both of which interfere with antigen presentation. Therefore, it appears that tumor antigen presentation by APCs play a key role in determining whether anti-tumor effector cells or suppressor cells are generated in response to a tumor challenge.

Effect of Anti I-J Antisera on Syngeneic Tumor Growth

The key role of suppressor cells in regulating the host immune response to tumor antigens has led us to study the effects of various anti-suppressor cell regimens on syngeneic tumor growth. The properties of tumor antigen specific Ts were shown in Table 1. Virtually any modality which depletes Ts will result in retardation of tumor growth. Thus treatment with anti-thymocyte sera results in inhibition of tumor growth, apparently by decreasing Ts [18]. The spleen contains the majority of Ts in a tumor-bearing animal, and splenectomy significantly retards tumor growth. Other workers have shown that splenic irradiation also delayed the growth of primary tumor inocula in syngeneic mice [15].

Suppressor cells, and their factors, are known to possess a cell surface structure (or structures) encoded in the J-J subregion of the mouse H-2 complex [26, 53, 85]. It is possible to produce I-J subregion-specific alloantisera by immunizing a given strain of mice with lymphoid cells from a strain that differs only at the I-J subregion. Administration of very small quantities (as little as 2 μl) of such an anti I-J alloantiserum results in profound suppression of tumor growth [25] (Fig. 1). The tumor inhibitory effects of anti I-J antisera cannot be removed by extensive absorbtion of sera with tumor cells. Therefore, it is unlikely that the antiserum is directly inhibiting tumor growth in vivo. Absorbtion on B10.BR(H-2^k) splenocytes does remove all the anti-tumor effects of anti I-J^k alloantiserum, while absorbtion on B10.D2(H-2^d) spleen cells has no effect. Thus it appears that anti I-J alloantiserum inhibits syngeneic tumor growth by interacting with lymphocytes, probably Ts, in the tumor-bearing host.

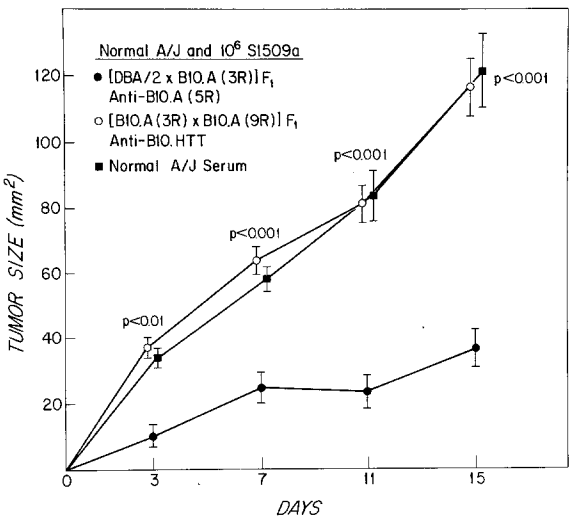

Fig. 1. Administration of anti I-J^k (—●—) results in suppression of S1509a tumor growth in A/J (H-2^a, K^k I^{k}D^d) mice, compared to treatment with anti I-J^s (—○—) or normal mouse serum (—■—). (adopted from Ref. 25)

Host-specific anti I-J serotherapy has been shown to suppress the growth of a variety of tumors in a number of mouse strains [64]. In studies using [A × B] F1 mice it has been shown that anti I-J sera reactive with either parental haplotype is equally effective in inhibiting tumor growth (Greene and Perry, unpublished observation). This supports the view that the products of I-J alleles are codominantly expressed on F1 suppressor lymphocytes. Anti I-J serotherapy also has a marked effect on the growth of UV-induced tumors in UV-irradiated mice [17]. As we have previously stated, such mice normally develop Ts which enhance the growth of their tumors. In UV-irradiated mice treated with anti I-J alloantisera such Ts do not develop.

Recently two laboratories have reported the identification of I-J specific monoclonal antibodies [40, 89]. We have obtained monoclonals WF8.C12.8 (anti I-J^k) and WF9.40.5 (anti I-J^b) from Dr. C. Waltenbaugh's laboratory, in order to investigate the in vivo effect of monoclonal anti I-J reagents on syngeneic tumor growth. Initial studies indicate that anti I-J^k monoclonal antibodies significantly inhibit S1509a growth in A/J (H-2^a, I-J^k) mice (Drebin, Waltenbaugh, and Greene in preparation). Anti I-J^b has no effect in S1509a growth in A/J mice. However in [A.BY × A/J]F1 (H-2$^{a/b}$, I-J$^{k/b}$) mice, both monoclonal anti I-J^k and anti I-J^b significantly inhibit S1509a growth. Thus monoclonal antibodies directed at I-J encoded cell surface structures may also significantly reduce tumor growth in mice whose suppressor T cells bear the appropriate I-J haplotype. The ability of monoclonal anti I-J to suppress tumor growth could eliminate certain theoretical arguments about the mechanism by which the anti I-J alloantisera suppresses tumor growth, such as the possibility of contaminating antiviral antibodies directly inhibiting tumor growth, since it will be possible to demonstrate whether the monoclonal possesses any anti-viral reactivity. If suppressor cell-specific surface molecules can be identified in man (presumably, though not necessarily encoded in the HLA-D region) monoclonal antibodies directed at such structures may prove a useful adjunct to the therapy of human malignant disease.

Anti I-J alloantiserum [66] and monoclonal antibodies [40, 89] have been shown to block the in vivo development of Ts specific for polypeptide antigens in genetically unresponsive strains of mice. Anti I-J alloantiserum is also reported to prevent schistosome-infected mice from suppressing their granulomatous response to the parasite, a Ts-mediated process [21]. A report by Meruelo et al., however, has shown that anti I-J alloantiserum increases mortality from AKR leukemia in syngeneic or semi-syngeneic mice [49]. Humoral immune responses are protective against AKR leukemia. Since the humoral anti-leukemic response is under control of an I-J region Ir-linked gene, it is believed that the anti I-J alloantiserum interacts with an I-J bearing T helper cell in this system. This clearly contrasts with the delayed growth of a variety of solid tumors where anti I-J antisera is administered [64], which presumably occurs by interaction of anti I-J with Ts or their factors.

Other modalities which inhibit Ts, such as low dose cyclophosphamide [35, 61], low dose irradiation [36], adult thymectomy [68], and immunization against blastic Ts [87] also inhibit or prevent syngeneic tumor growth. It is of interest that experimental adoptive immunotherapy of established tumors is generally without effect [70] unless the tumor-bearing animals receive cyclophosphamide or radiation treatment to deplete Ts prior to effector lymphocyte infusion [12, 23]. Anti I-J antibodies (and its human equivalent) may be a particularly useful adjunct to adoptive immunotherapy, since they are more specific and less toxic than other methods of depleting Ts [11].

Tumor Antigens and Transforming Genes

The biochemical characterization of tumor antigens would greatly increase our understanding of the nature of the anti-tumor immune response. The difficulty in the immunochemical study of tumor antigens is primarily a problem of specificity [59]. Tumor cells have been shown to possess viral antigens [9], embryonic antigens [14], and alloantigen-like structures [38]. It seems clear that at least some types of tumor cells possess novel antigens related to the transformed state. The common UV-induced antigen, mentioned previously, is one such structure. We are currently investigating the relationship between structures present on the cell surface of transformed cells and structures encoded by genes that are linked to the transforming event itself. These studies have been pursued using polyoma transformed cells, in collaboration with T. Benjamin, and in chemically transformed and transfected cells in collaboration with R. A. Weinberg.

Polyoma is a double stranded DNA virus capable of either cell transformation or lytic infection [39]. Polyoma infection of normal adult mice is not associated with development of neoplasia, but infection of neonatal or athymic nude mice [84] results in the development of lethal tumors. Thus polyoma is oncogenic in the strain which it naturally infects, and its oncogenic potential is regulated by the host's immune response.

The entire DNA sequence of polyoma virus is known [39]. The so-called early gene region contains the genetic information necessary for transformation [75]. This region is known to encode three principal peptides, known as T antigens. Large T (100k), middle T (55k), and small T (22k) antigens are observed in cells infected

with or transformed by polyoma virus [37]. Large T exists primarily in the nuclear membrane, middle T in the plasma membrane, and small T in the cytoplasm. All three T antigens are encoded in the same DNA; their differences arise from the RNA splicing event following transcription of a single mRNA [39]. All three T antigens share the same amino terminus. It has been shown that viral mutants which are unable to transform cells have a mutation in the region encoding middle T and small T [75]. Mutations in the large T region do not prevent cell transformation. Middle T antigen possesses, or is closely associated with, an in vitro tyrosine-specific protein kinase activity [13]; this unusual kinase characteristic is associated with the transforming proteins of many retroviruses as well [47]. Kamen and associates recently cloned middle T mRNA specific cDNA, and showed that this cDNA alone leads to middle T antigen expression and cell transformation, when it is introduced into cells by appropriate means [88]. Thus the polyoma middle T antigen appears to be encoded by the viral gene responsible for cell transformation, and may be involved in the transformation event itself.

The localization of the polyoma transforming potential to a single gene, and the fact that polyoma-transformed cells are subject to immune surveillance prompted us to investigate whether structures recognized by polyoma-specific immune effector cells are related to structures encoded by the polyoma-transforming gene [30]. Table 7 demonstrates that polyoma-specific cytotoxic T lymphocytes (CTL) can be generated by appropriate immunization and that these CTL recognize viral determinants encoded in the polyoma early region. These CTL have the Ly $1-2+$ phenotype and are H-2 restricted. Dr. Benjamin is currently pursuing a more detailed study of the structure(s) encoded in the viral early region which are recognized by CTL. It appears that in a well characterized viral transformation system, a tumor antigen recognized by anti-tumor CTL is encoded or linked to the genetic region responsible for transformation. Tevethia et al. have demonstrated a similar linkage between tumor antigen expression and the viral-transforming region in SV40-transformed cells [86].

The immune response against carcinogen-induced tumors is generally not as strong as that against viral tumors [43], and the tumor antigens on chemically transformed cells have been more difficult to study biochemically. The recent achievement of transformation of mouse fibroblast cell lines by transfection of DNA

Table 7.

Effector cells	Target cell	% Specific lysis at Effector: Target = 100 : 1
B10.D2 anti Py B10.D2	Py B10.D2 ($H\text{-}2^d$)	51.6
B10.D2 anti Py B10.D2	Sv B10.D2 ($H\text{-}2^d$)	19.2
B10.D2 anti Py B10.D2	Sv B10.D2 infected with wild type polyoma 20 h prior to assay	53.2

Recognition of polyoma virus early region encoded antigen(s) by polyoma-specific CTL
Cell types: Py B10.D2 = polyoma-transformed B10.D2 fibroblast
Sv B10.D2 = SV-40 transformed B10.D2 fibroblast

from chemically transformed cells [8, 72] has made it possible to begin to study chemically activated cellular transforming genes. If tumor antigens are related to these transforming genes, then chemically induced tumors should cross-react immunologically with cells transformed by transfection of homologous transforming genes, but not with cells transformed by irrelevant transforming genes. In at least one tumor system this appears to be the case (Drebin, Shilo, Weinberg, and Greene, in preparation). The generality of the linkage between cellular transforming genes and tumor antigens remains to be proven. However, evidence in favor of such a relationship is accumulating in both virally and chemically transformed systems. It may be that chemical carcinogenesis, like viral carcinogenesis, involves the presence in the cell membrane of specific proteins necessary for transformation. These proteins, if recognizable by the immune system, could serve as tumor-specific antigens. The existence of a linkage between transforming genes and tumor antigens would provide a rationale for the existence of tumor-specific antigens on transformed cells.

Conclusion

The cellular pathways involved in regulating the immune response to tumor antigens are shown in Fig. 2. Different subsets of lymphocytes are capable of responding to syngeneic tumor antigens. Antigen presentation by antigen presenting cells, in the context of cell surface I-A subregion encoded structures is necessary for activation of anti-tumor effector T lymphocytes. In the S1509a tumor system,

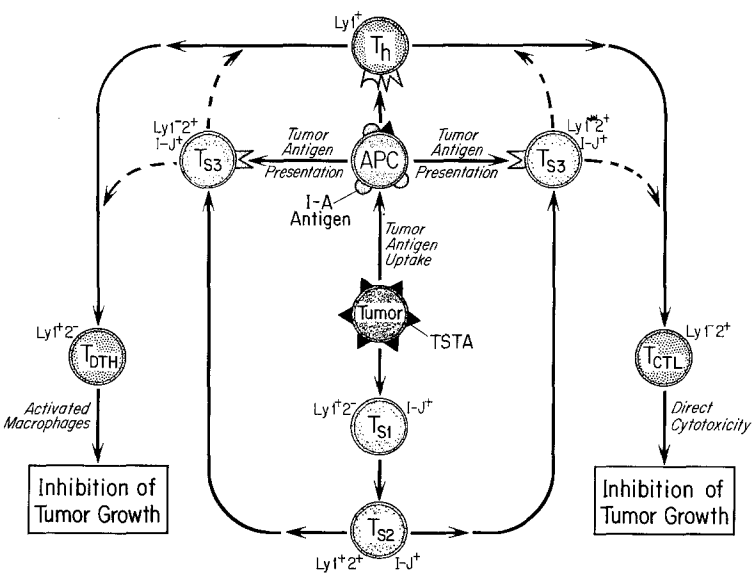

Fig. 2. Regulation of the immune response to tumor antigens. *Solid lines* indicate stimulatory cell to cell interactions. *Broken lines* indicate inhibition of anti-tumor T effector cells by suppressor T cells

lymphocytes of the Lyt 1+2− phenotype predominantly respond to tumor antigens in vivo and in vitro. The administration of anti I-A antisera, UV irradiation, or IV antigen prevents effective antigen presentation to Ly 1+2− effector cells, and diminishes the anti-tumor immune response through the generation of suppressor T cells. There are actually several subsets of suppressor T cells, which interact via idiotypic and anti-idiotypic suppressor factors. Soluble tumor antigen leads to the generation of Ts which inhibit adaptive T cell-mediated immune response, and the same shed antigen may influence non-adaptive non-T cell mediated responses. Regimens which block suppressor T cell activity, particularly administration of specific anti I-J antibodies, result in marked reduction of in vivo tumor growth.

While the biochemical characterization of tumor antigens remains somewhat imprecise, the functional regulation of immune responses to these antigens is becoming increasing well understood. Evidence is beginning to accumulate which supports the idea that some genes encoding tumor antigens are closely linked to, or identical with, genes responsible for malignant transformation. Additional study of the relationship between tumor antigens and transforming genes will help clarify both the biochemical nature of tumor antigens and the regulation of the immune response to these antigens.

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