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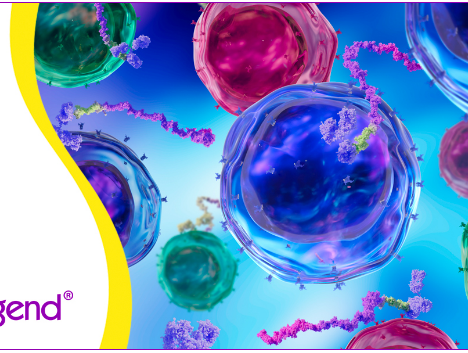

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GENETIC MAPPING OF AN H-2-ASSOCIATED ANTIGEN EXPRESSED ON REGULATORY T CELLS[1]

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T lymphocytes that serve regulatory functions in the generation of effector T cells to alloantigen and to altered syngeneic cells express a distinguishing H-2-associated cell surface marker that we have termed Ha. Genetic mapping studies with the B10.A(2R), B10.A(4R), B10.A(5R), and LG/Ckc lines of mice have delineated the locus determining the expression of Ha to the right of H-2K and left of H-2IB *or* within the I-A region. Thus, these regulatory T lymhocytes express Ia antigens.

Murine lymphocytes can be distinguished from each other by their expression of different cell surface markers. Thymus-dependent lymphocytes (T cells) can be divided into subclasses that play different functional roles in the generation and/or regulation of immune responses based on their different expression of allotypic markers encoded by the Ly, Qa, and H-2I loci (1–3). Antigen-specific cells within some of the functional subclasses can also be distinguished through idiotypic markers (4, 5). Thus, cell surface markers may eventually allow one to identify virtually all clones of antigen-reactive T cells through idiotypic markers and then to identify their functional capacities through allotypic markers.

We have been studying the role of T cells that express allodeterminants encoded by loci within the major histocompatibility complex (MHC),[2] H-2, in the generation of cytotoxic T cells to alloantigens. Expression of I-region-associated antigens, Ia, is determined by at least four genetically separable loci within the H-2I complex: I-A, I-J, I-E, and I-C. Approximately 90% of B lymphocytes express I-A and I-E, C-region-associated antigens. B lymphocytes may also be separable into distinct functional subpopulations on the basis of preferential expression of some I-A region-encoded antigens (6). T lymphocytes can readily be classified into functional subclasses based on their differential expression of Ia antigens associated with different I-loci, particularly the I-J region (3, 7). Suppressor T lymphocytes that are detectable in a variety of experimental systems can be distinguished from the majority of T lymphocytes through the I-J-associated cell surface marker. T lymphocytes expressing I-J-coded antigens represent a minor fraction of the total T cell repertoire and are most readily demonstrated in functional assays (3). In general, direct detection of Ia markers on "resting" T lymphocytes has been difficult. Activated T lymphocytes, however, have led successfully to the detection of T-associated Ia antigens (8–10).

We have utilized functional assays to demonstrate the presence of an H-2-associated differential antigen, Ha, on normal T lymphocytes that are required for the generation of T cell responses (8). We have demonstrated that cells expressing the Ha marker play a regulatory role in the development of cellular immune responses (11). We present data here demonstrating that the Ha marker expressed by these regulatory T lymphocytes is encoded in a region to the right of H-2K and to the left of H-2IB; i.e., within what is *presently* known as the "I-A region." Regulatory T lymphocytes that express the "I-A region"-associated antigen are also required for the generation of syngeneic or altered self effector T cells.

MATERIALS AND METHODS

Animals. B10.A(4R) mice were raised in our laboratory from breeding stock provided by Dr. J. Stimpfling, Great Falls, Montana. A.SW mice were generously provided by Dr. D. B. Amos, Durham, North Carolina. C57BL/10, B10.D2, B10.A(2R), and LG/Ckc were purchased through The Jackson Laboratory, Bar Harbor, Maine.

Antisera. The (A × B10.A)F_1 anti-B10.A(5R) serum was provided through the resources branch of N.I.A.I.D., Bethesda, Md. Anti-Thy-1.2 serum was produced in (AKR × RF)F_1 mice against C58 thymus cells.

Sensitization in vitro. Responding strain lymph node cells and stimulating strain spleen cells were prepared as previously described (11). Irradiation was from a ^{137}Cesium source. Microplates containing 7.5×10^5 cells of each, responders and stimulator, in 0.2 ml/well of RPMI 1640 culture medium containing 10% human serum, 0.01 M HEPES[2] buffer, 50 μg L-arginine, 75 μg L-glutamine, 100 units penicillin G, and 75 μg kanamycin sulfate were incubated for 5 days in a humidified atmosphere of 5% CO_2. The cells from 10 replicate wells were then pooled, washed, counted, and set up at a number of concentrations against ^{51}Cr-labeled EL-4 target cells (H-2^b) or against ^{51}Cr-labeled and TNP-coupled P815-X2 (H-2^d) cells and assayed as described previously.

Cells in which the incorporation of ^{3}H thymidine was evaluated were cultured in triplicate either alone, with allogeneic irradiated cells, or with 25 μg of *Escherichia coli* lipopolysaccharide (LPS). The cultures were pulsed with 1 μCi ^{3}H-thymidine (sp. act. = 6.0 C/mmole; Schwarz/Mann) for 18 hr before harvesting through a MASH II automated harvester.

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[2] Abbreviations used in this paper: Ha, H-2-linked helper T cell-associated antigen; NMS, normal mouse serum; MHC, major histocompatibility complex; HFS, helper factor supernatants; LPS, lipopolysaccharide derived from *Escherichia coli*, No. 011:B4; HEPES, *N*-2-hydroxyethylpiperazine-*N*'-2-ethanesulfonic acid; TaF, augmenting T cell factor.

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TNP modification. Irradiated B10.D2 nucleated spleen cells or P815-X2 (H-2^d) tumor target cells were conjugated with TNP following essentially published protocols (12, 13). Cells were incubated for 10 min at 37°C in 10 mM phosphate-buffered saline, pH 8.0, that contained 10 mM 2,4,6-trinitrobenzene-sulphonic acid. Thereafter, the spleen cells were washed in RPMI 1640 medium plus 10% human serum and prepared for culture. The TNP-altered P815-X2 targets were washed in RPMI 1640 plus 10% calf serum and labeled with ^{51}Cr as previously described.

Absorption. Thymus and spleens were removed from 14 mice of each strain. The cells were suspended in 0.6 ml of RPMI 1640 medium, and 0.2 ml of antiserum was added to each. Absorptions were performed for 30 min on ice. The cells were pelleted by centrifugation in a serofuge, the supernatant antiserum was removed, and the volume of each was adjusted to 1.0 ml for a 1/5 final dilution. Absorptions with EL-4 T lymphoma cells were carried out similarly but with 10^9 cells per 0.1 ml of antiserum.

Antiserum treatments. Lymph node cells at 15×10^6/ml were treated for 15 min at 37°C with normal mouse serum (NMS) or (A × B10.A)F_1 anti-B10.A(5R) diluted 1/5. An equal volume of 1/10 diluted rabbit serum that had been screened for low toxicity and high complement (C) activity was added, and the cell suspensions were further incubated for 30 min before washing three times. Anti-Thy-1.2 serum was used at a 1/25 dilution, and 5×10^7 cells were treated in 0.5 ml. A two-stage cytolysis procedure that involved a wash step between antiserum and C treatments was followed when cells were treated with absorbed serum.

Helper factor supernatants. Supernatants were derived from 6-hr incubation mixtures of 3- to 5-day allogeneically activated cells plus fresh stimulating strain cells. The protocol for the two-step tissue culture procedures have been described in detail previously (14).

RESULTS

The (A × B10.A)F_1 anti-B10.A(5R) serum utilized in these studies theoretically could contain antibodies directed against antigens coded within H-$2K^b$, I-A^b, and I-B^b regions. The antiserum also cross-reacts with some but not all T and B lymphoid cells of the H-2^d haplotype; therefore, H-2^d cells and recombinants thereof as well as H-2^b recombinants can be utilized to define both the functional nature of lymphoid subclasses that express the antigens and the genetic region controlling their expression (Table I).

Treatment of B10.D2 strain lymph node cells with this antiserum plus C results in the removal of a subpopulation of T lymphocytes that are required for the generation of killer cells during the subsequent 5-day culture with stimulating cells. Absorption of the antiserum with B10.A(2R) lymphoid cells whose H-2^k, I-A^k, and I-B^k regions were derived from the antibody producers' H-2^a haplotype does not result in the nonspecific absorption of the anti-T cell activity directed against the B10.D2 cells (Fig. 1). Hence, B10.D2 cells treated with antiserum absorbed with B10.A(2R) have a greatly depressed ability to generate killer cells. The addition of exogenous help presented by our helper factor supernatants (HFS) (14) to these antiserum-treated cells results in the generation of killer cells equivalent to levels observed with cells treated with antiserum that had been absorbed with the target strain B10.D2 cells (Fig. 1). These data substantiate our earlier findings demonstrating that the cross-reactive anti-T cell activity within B10.A anti-B10.D2 serum was directed against a helper or regulatory T cell rather than prekiller cells (11). Thus, the (A × B10.A)F_1 anti-B10.A(5R) serum is similar to the B10.A anti-B10.D2 serum in that it contains antibody activity directed against the Ha marker on helper or regulatory T cells.

Using the appropriate recombinants, we have now been able to map the gene(s) controlling the expression of the Ha marker. Absorption with B10.A(4R) cells did not remove the anti-Ha activity against B10.D2 cells (Fig. 1). The B10.A(4R) has the I-B^b region in common with the B10.A(5R) immunizing donor strain. The Ha marker, therefore, must be coded in a region to the left of I-B (Table I). These results were corroborated through direct testing of the recombinant strain cells (Fig. 2). Genetic mapping of the T cell antigen, Ha, was further accomplished with the LG/Ckc recombinants. Treatment of lymph node cells from the B10.A(4R) and LG/Ckc lines with antiserum and C before sensitization *in vitro* did not result in a decrease in the generation of killer cells (Fig. 2*A* and 2*D*, respectively). The B10.D2 line served as a positive control for the antiserum (Fig. 2*C*), whereas A.SW (H-2^s) served as a negative control in these experiments (Fig. 2*B*). The LG/Ckc line has the same H-$2K^d$ phenotype as that of the cross-reactive B10.D2 line. The lack of effects on the responses of LG/Ckc and B10.A(4R) indicated that the region coding for the Ha regulatory T cell marker is located to the right of H-2K and to the left of I-B. The only locus presently defined in this region is Ia-1 (I-A).

TABLE I

Genetic localization of the Ha helper cell marker[a]

Strain	H-2 Allele	H-2 Regions								
		H-2K	H-2I					H-2S	H-2G	H-2D
			A	B	J	E	C			
B10.D2	H-2^d	d	d	d	d	d	d	d	d	d
LG/Ckc	H-2^{df}	d	f	f	(f)	f	f	f	f	f
B10.A(4R)	H-2^{h4}	k	k	b	b	b	b	b	b	b
B10.A(5R)	H-2^{i5}	b	b	b	k	d	d	d	d	d
B10.A	H-2^a	k	k	k	k	d	d	d	d	d
B10.A(2R)	H-2^{h2}	k	k	k	k	k	d	d		b
A.SW	H-2^s	s	s	s	s	s	s	s	s	s

[a] Taken from Klein *et al.* (15).

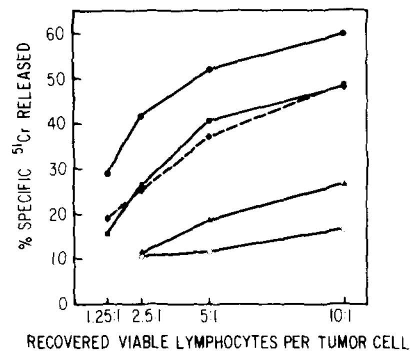

Figure 1. Effect of (A × B10.A) F_1 anti-B10.A(5R) serum treatment on the generation of T cell-mediated response to alloantigens. B10.D2 strain lymph node cells were treated with rabbit C plus normal mouse serum (●——●), or (A × B10.A) F_1 anti-B10.A(5R) serum absorbed with B10.A(2R) cells (○——○), B10.A(4R) cells (▲——▲), or B10.D2 cells (■——■). Helper factor supernatants produced from B10.D2 plus C57BL/10 (2000 R) mixed lymphocyte activated cells (14) were added to cultures of B10.D2 cells pretreated with antiserum absorbed with B10.A(2R) cells (◆——◆). Killer T cell activity was evaluated after 5 days in culture with irradiated C57BL/10 nucleated spleen cells.

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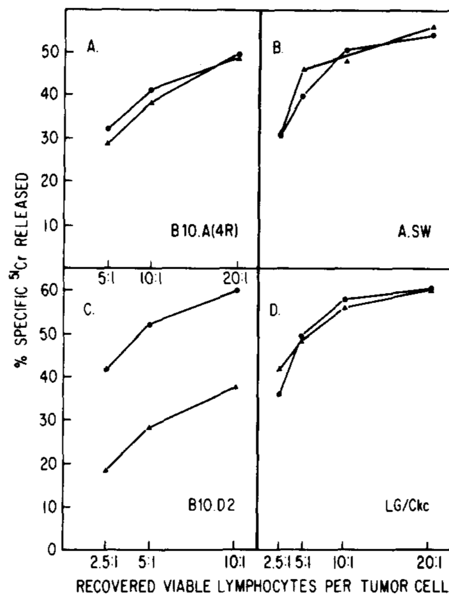

Figure 2. Genetic mapping of the Ha, helper T cell-associated marker. Lymph node cells from the respective strains were treated with rabbit C and NMS (●——●) or (A × B10.A) anti-B10.A(5R) serum (▲——▲) then cultured with C57BL/10 irradiated spleen cells for 5 days. EL-4 tumor cells labeled with ^{51}Cr served as targets for the detection of killer T cell activity.

It is possible, however, that the region between H-2K and H-2IB carries several loci, including at least one that codes for Ia determinants expressed on B cells and/or macrophages and one that codes for Ia determinants expressed on T cells. To determine whether we could differentially absorb out antibody activity directed against T cells, we chose to absorb the (A × B10.A)F_1 anti-B10.A(5R) serum with EL-4 T lymphoma cells, since we had observed that a proportion of these cells were lysed by this antiserum plus C. B10.D2 cells were subsequently treated with the EL-4 absorbed serum, unabsorbed antiserum, and NMS plus C. The remaining viable cells were then cultured with allogeneic cells to determine levels of T cell responses or with the B cell mitogen, LPS. The data obtained (Table II) suggest that indeed there is a differential absorption of the anti-T cell activity with the EL-4 cells, since the responses in the MLR were increased over unabsorbed serum by 57% in one experiment and 76% in the second. The slight increase in LPS responses, 25% and 18%, may be due to some nonspecific absorption of the anti-B cell activity or some degree of T cell response to this particular LPS preparation (8). Definitive proof of distinct loci coding for T cell and B cell Ia determinants, however, must await the description of appropriate recombinant lines or hybridoma monoclonal antibodies.

Regulatory T cells that function in the generation of cytolytic effectors for syngeneic and H-2 restricted TNP-modified cells have the Ly 1^+, 2^+, 3^+ phenotype, whereas amplifiers of allogeneic responses are Ly-1^+ (16). It was of interest, therefore, to determine whether regulatory T cells that express the Ha marker were also required for the generation of killers for altered self antigens. Indeed, treatment of B10.D2 lymph node cells before sensitization with TNP-modified B10.D2 spleen cells results in the removal of a subpopulation required for the generation of killers to syngeneic TNP-modified targets (Fig. 3). Furthermore, the addition of helper factor supernatants to the anti-Ha serum-treated cells substituted for the functions of the lysed Ha^+ cells, whereas non-T cells (those remaining after lysis with anti-Thy-1.2 cells) did not (Fig. 4), thus demonstrating that again in the TNP-modified self system the Ha^+ cell functions are attributable to regulatory T cells.

DISCUSSION

The Ha marker is an I-region-encoded antigen expressed on T lymphocytes that have regulatory functions in the differentiation of prekiller cells for allogeneic and altered-self syngeneic antigens. The Ha marker maps within the I-A region. Absorption studies with "enriched" B cells (data not presented) as well as with the T cell lymphoma, EL-4, suggest that the anti-Ha activity is distinct from anti-Ia.8 and other B cell-associated Ia markers, such as Ia.9,11. Definitive proof that the I-A region can be divided further into two or more loci or alternatively that Ha is identical to Ia antigens already defined in this area, such as Ia.8, must await the production of monoclonal anti-Ha antibodies from selective hybridomas that we are attempting to isolate. Hybridoma production of anti-Ha should prove very useful, since some of the difficulties that arise during the production of anti-Ly sera are also encountered during alloimmunization for anti-Ha (17). For example, recipients of immunizing cells need to be screened individually for anti-Ha production, since some mice produce relatively good responses and

TABLE II

Differential absorption of anti-T and anti-B cell activities

Additions to Cultures	Responder B10.D2 LNC Pretreatment		
	NMS	(A x B10.A)F_1 anti-B10.A(5R)	
		Unabsorbed	Absorbed with EL-4
	average cpm ^{3}H-thymidine incorporation		
Experiment 1			
None	447	404	337
MLR (C57BL/10 2000 R)	64,034	10,736 (84%)[a]	46,996 (27%)
25 μg *E. coli* LPS	11,294	413 (100%)	3,035 (75%)
Experiment 2			
None	2,103	800	723
MLR (C57BL/10 2000 R)	85,751	9,309 (90%)	72,707 (14%)
25 μg *E. coli* LPS	10,718	539 (100%)	2,245 (82%)

[a] Figures in parentheses are percent reduction of response as compared with the NMS response; i.e.:

$$100 \times \frac{\text{cpm antiserum-treated MLR (or LPS)} - \text{no addition}}{\text{cpm NMS-treated MLR (or LPS)} - \text{no addition}}$$

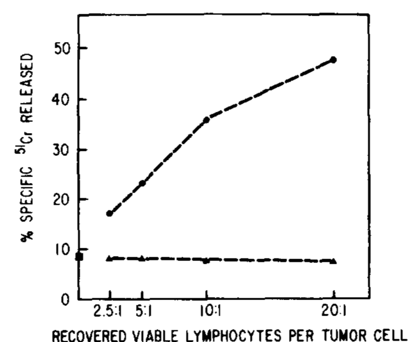

Figure 3. Effect of anti-Ha serum on the generation of syngeneic killer T cells to TNP-altered cells. B10.D2 lymph node cells were pretreated with rabbit C plus NMS (●-----●) or (A × B10.A)F_1 anti-B10.A(5R) serum (▲----▲). TNP-altered P815-X2 tumor cells served as targets in the killing assay. Spontaneous release of ^{51}Cr-labeled cells after 3-hr assay is indicated (■).

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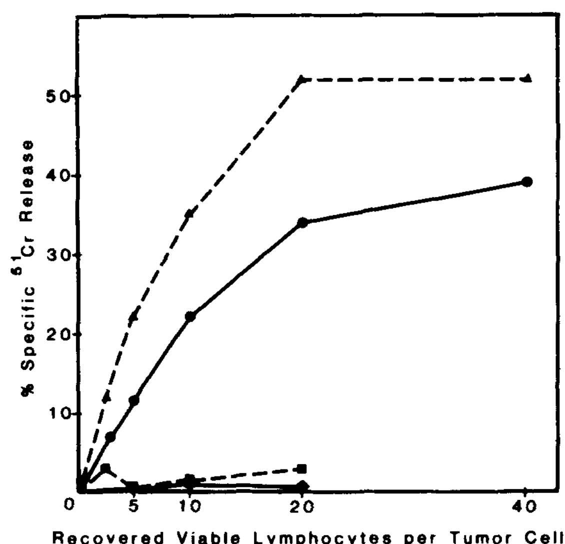

Figure 4. Effect of HFS and non-T cells on the generation of syngeneic killer T cells in cultures depleted of Ha$^+$ cells. B10.D2 lymph node cells were pretreated with rabbit C plus (A × B10.A)F anti-B10.A(5R) serum and cultured with either HFS (●——●) or with anti-Thy-1.2 pretreated cells (■- - -■). Anti-Thy-1.2 pretreated cells did not generate killer cells when cultured with HFS (◆——◆) nor did they suppress HFS effects in mixtures with those cells remaining after lysis with (A × B10.A)F$_1$ anti-B10.A(5R) serum (▲----▲). TNP-altered and irradiated B10.D2 cells served as the stimulus in all of these cultures. HFS were derived from two-step cultures of B10.D2 plus C57BL/10 (2000 R) allogeneic cell mixtures.

others do not. Also, absorptions with lymphoid cells from the antibody producer strains result in an enhancement of anti-Ha activity (data not presented).

Tokuhisa *et al.* (18) have suggested that the I-A region may consist of at least two loci based on their studies with an antigen-specific augmenting T cell factor (TaF). Although augmenting effects of TaF were I-A restricted, it is possible that A.TH anti-A.TL antisera could also have reacted with T cell Ia antigens associated with I-E (19) rather than a product of a new locus between H-2K and Ir-1B. Cross-reactive anti-Ia sera similar to those utilized in our studies did not remove TaF activity (18). Further evidence for the possible subdivision of the I-A region comes from the recognition of an Ia determinant that is expressed on only a proportion of B cells (6). This B cell antigenic determinant has a different strain distribution than does the Ha marker, and the B cell determinant does not cross-react with the H-2^d haplotype (6). Thus, at least three cell surface markers have been mapped to the I-A region of the H-2^b haplotype.

The presence of I-A region-associated antigens on regulatory cells has also been suggested from studies *in vivo* of syngeneic tumor immunity. Perry *et al.* (20) demonstrated that anti-Ia serum depressed primary responses to a syngeneic tumor and that secondary responses as well as the ability to transfer secondary immunity to naive recipient could be depressed by prior treatment of immune mice with antiserum that reacts with I-A. Taken together, these data strongly suggest that T cells that express I-A-associated antigens play a major role in immuno-regulation.

The existence of specific I-A-associated antigens on regulatory T cells might be relative to the apparent I-A region restrictions observed in T helper-macrophage interactions (21–23). This locus may well control helper T cell differentiation or serve as a receptor for cell-cell interaction. It is clear from our own studies that Ia-bearing nonimmune T cells function in the regulation of the production of soluble proteins that serve as a second signal for the differentiation of pre-effector cells to killer T cells (11, 14, 24).

The effect of anti-Ha serum on the generation of TNP-coupled syngeneic killer cells is of particular interest, since their development may represent a primary event in contrast to allogeneic killing (25), and since the Ly phenotype of these prekillers differs from that required for allogeneic killing (16). Thus, Ha-bearing T cells are required for further differentiation of both Ly 1,2,3$^+$ and Ly 2,3$^+$ prekiller cells.

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