EPITOPES ASSOCIATED WITH THE MHC RESTRICTION SITE OF T CELLS

II. Somatic Generation of Iat Epitopes on T Cells in Radiation Bone Marrow Chimeras

By YOSHIHIRO ASANO, and TOMIO TADA

From the Department of Immunology, Faculty of Medicine, University of Tokyo, Tokyo, Japan

One of the fundamental questions in current immunology is concerned with the understanding of molecular basis of the MHC restriction of T cells. This includes the T–accessory (Acc)[1] cell, T–B, and T–T cell interactions, which altogether construct the immunoregulatory circuit (1, 2). Even though the basic structure of the antigen receptor of T cells (TcR) has been determined, the molecular elements involved in the MHC restriction are still largely unknown (3–9).

Our previous reports demonstrated that some of the mAb putatively directed to the I region of MHC, but lacking the reactivity to known class II antigenic epitopes (anti-Iat), can block the MHC-restricted T–B cell interaction by acting on T cells but not on B and Acc cells (10–12).[2] The specificity of these antibodies was found directed to the restriction elements of T cells, as the T cell function restricted to one parental MHC but not to the other in the F_1 T cell population was inhibited by these antibodies (12).[2] This non-codominant but probably clonal expression of these epitopes on F_1 T cells led us to consider that these epitopes are associated with the MHC restriction site of T cells. Anti-Iat mAb used in the previous paper were able to eliminate up to 70% of the H-2-restricted helper activity, and can enrich Th cells 100 times by a positive selection. This suggested that Iat epitopes are distributed among various antigen-specific T cell clones of MHC-restricted Th with a limited heterogeneity.[2]

It has been well documented that the MHC-restriction specificities of T cells are not solely determined by the I region genotype of the bone marrow stem cells, but are adaptively acquired by the early-developing T cells in the thymus in the radiation bone marrow chimera (13–17). If our postulate that Iat epitopes are not the direct product of I region genes but are associated with the restriction

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[1] *Abbreviations used in this paper:* Acc, accessory; Iat, I region–associated T cell antigen; TcR, T cell receptor.

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element of T cells that sees the class II antigen is correct, such epitopes should also be adaptively acquired under the chimeric condition. We have, therefore, constructed a number of radiation bone marrow chimeras of different stem cell origins, and the parallel examination was made on the relationship between the MHC restriction and expression of the given Iat phenotype. The results presented in this communication indicate that Iat phenotype on Th cells in chimeras is adaptively generated under the influence of environmental MHC rather than the genotype of stem cells. This opens a vista to study the inducible molecular elements associated with the TcR determining the MHC restriction of T cells.

Materials and Methods

Animals

C57BL/10 (B10), B10.A, B10.BR, C57BL/6 (B6), C3H, and (B6 × C3H)F_1 (B6C3F_1) mice were purchased from the Shizuoka Agricultural Cooperative Association for Laboratory Animals, Hamamatsu, Japan. B10.A(3R), B10.A(4R), (B10 × B10.A)F_1, and C3H.SW mice were bred in our animal facility.

Chimeras

Chimeras used in this study were prepared as previously described (18), and are designated as bone marrow donor → irradiated recipient. Chimeras were used no earlier than 8 wk after irradiation and reconstitution. Spleen cells of chimeric mice were examined to ascertain their donor origin by the cytotoxicity assay, with only negligible cells (<5%) killed by antibodies against the host H-2.

Antigens

Keyhole limpet hemocyanin (KLH) (Calbiochem, San Diego, CA) was conjugated with 2,4,6-trinitrobenzene sulfonic acid (Pierce Chemical Co., Rockford, IL) (TNP-KLH) as previously described (18). The substitution rate was 20 TNP residues per 100 kD KLH.

Antibodies

Monoclonal antibodies reactive with I region–controlled polymorphic determinants of H-2^k haplotype that are uniquely expressed on T cells (anti-Iat^k; 1L9, 2L2, and 74L) are those described in previous papers (10–12).[2] These anti-Iat^k are the products of hybridomas derived from spleen cells of A.TH immune to A.TL lymphoid cells, and have been selected in the criteria that they can react with an augmenting T cell hybridoma (20) and some functional T cells but not with B cells and macrophages of H-2^k strains. Ascites containing monoclonal antibodies were produced in BALB/c *nu/nu* mice. An anti-L3T4a antibody is obtained as the culture supernatant of hybridoma GK1.5 which had been made available by Dr. F. W. Fitch, University of Chicago, Chicago, IL (20) and was provided by Dr. R. J. Hodes, National Institutes of Health, Bethesda, MD. An anti-H-2^b [(B10.A × A/J)F_1 anti-B10] antiserum was kindly provided by Dr. D. H. Sachs, NIH. An anti-H-$2K^k$ monoclonal antibody (11-4.1) (21) as culture supernatant was obtained from the hybridoma provided by the Salk Institute Cell Distribution Center, San Diego, CA. Anti-H-2^k and anti-H-2^b antisera were prepared by repeated reciprocal immunization of C3H.SW and C3H with partner spleen. Cytotoxic treatment of T cells was carried out at 10^7 cells/ml with the appropriately diluted antibody as previously described.[2]

Immunization

Mice were immunized intraperitoneally with 100 μg of KLH, or TNP-KLH in CFA (Difco Laboratories, Detroit, MI). Spleen cells were taken at 3–8 weeks after the immunization. The immunization of fully allogeneic and parent → F_1 chimeras were performed by an intraperitoneal injection of antigen-pulsed irradiated Acc cells of appropriate F_1 origin, as described previously (22).

TABLE I

Iat^k Epitopes Are Expressed on H-2^k-restricted But Not on H-2^b-restricted F_1 T Helper Cells

Th cells treated with:	IgG anti-TNP PFC/culture	
	B10 B cells + F_1 Th cells	B10.BR B cells + F_1 Th cells
C alone	1,411 ± 148	1,541 ± 138
Anti-H-2^k + C	44 ± 23	24 ± 16
Anti-H-2^b + C	38 ± 22	24 ± 16
1L9 + C	1,453 ± 195	1,497 ± 241
2L2 + C	1,651 ± 168	614 ± 105
74L + C	1,401 ± 188	312 ± 49
GK1.5 + C	0	0

10^6 KLH-primed B6C3 F_1 Th cells were treated with indicated antibody + C. The residual cells were cocultured with 3×10^6 TNP-primed B10 or B10.BR B cells in the presence of 1 ng/ml TNP-KLH. B cells alone gave no PFC.

Preparation of Cells In Vitro Antibody Responses

B cells. A fraction containing B cells and accessory cells was obtained by depleting T cells from TNP-KLH-primed spleen cells by the treatment with a T cell specific rabbit anti-mouse brain serum (RAMB) + complement (C) in a manner described previously (18).

T cells. The spleen cell fraction containing T cells was obtained as spleen cells nonadherent to anti-mouse immunoglobulin-coated plastic dishes (18).

Acc cells. Unprimed spleen cells were depleted of T cells by the treatment with RAMB + C and were irradiated at 3,000 rad. The cells were pulsed with antigen by incubating in RPMI 1640 medium containing 10% FCS and 100 μg/ml KLH, and were used as antigen-pulsed accessory cells (22).

Culture Conditions for the In Vitro Antibody Response

The in vitro secondary antibody formation was performed as described previously (18). Briefly, all cultures were performed in a volume of 2 ml per 16-mm-diam flat-bottomed well (3524; Costar, Cambridge, MA) and were incubated for 5 d at 37°C in 5% CO_2 humidified air atmosphere. Medium used was RPMI 1640 supplemented with 2 mM L-glutamine, 1 mM sodium pyruvate, nonessential amino acids, 5×10^{-5} M 2-ME, and 10% FCS. Harvested cells were assayed for plaque forming cells (PFC) with TNP-conjugated sheep erythrocyte (18). All points shown in each experiment represent the arithmetic mean IgG PFC of identical triplicate cultures.

Results

Iat^k Epitopes Are Expressed on H-2^k-restricted But Not on H-2^b-restricted F_1 T Helper Cell Population. Evidence that Iat epitopes are linked to the MHC restriction specificity was confirmed by treating the KLH-primed B6C3F_1 T cells with anti-Iat^k + C. The cells were then cocultured with TNP-primed B10 or B10.BR B cells to induce an in vitro secondary antibody response (Table I). The helper activity of F_1 T cells restricted to H-2^k (B10.BR) B cells was largely eliminated by the treatment with two of the anti-Iat mAb, 2L2 and 74L, but not with another anti-Iat, 1L9, which was capable of reacting with an Iat$^+$ T cell hybridoma (10, 19). These antibodies did not affect the H-2^b-restricted helper function of the same F_1 T cell population. The results indicate that Iat^k epitopes

TABLE II

Adaptive Expression of Iat^k on T Cells of F_1 → Parent Chimera

Th cells treated with:	IgG anti-TNP PFC/culture	
	B10 B cells + F_1 → B6 Th cells	B10.BR B cells + F_1 → C3H Th cells
C alone	2,509 ± 266	1,388 ± 184
Anti-H-2^k + C	0	0
Anti-H-2^b + C	0	0
1L9 + C	2,087 ± 184	1,645 ± 60
2L2 + C	1,906 ± 105	553 ± 31
74L + C	1,881 ± 137	338 ± 127

10^6 KLH-primed Th cells of F_1 → B6 or F_1 → C3H chimera origin were treated with indicated antibody + C. The residual cells were cocultured with 3×10^6 TNP-primed B10 or B10.BR B cells in the presence of 1 ng/ml TNP-KLH. B cells alone gave no PFC. F_1 → B6 or F_1 → C3H Th cells provided no help to nonrecipient type parental B cells.

are expressed only on T cells restricted to H-2^k B cells in the secondary antibody response.

Expression of Iat Epitopes on F_1 → Parent Chimeric Helper T Cells Is Determined by Host Environment. Because the MHC restriction specificity of T cells is known to be determined by the thymic environment where T cells undergo early development, the mode of expression of Iat on T cells in the radiation bone marrow chimeras was examined. For this purpose, a variety of bone marrow chimeras were prepared, as in Materials and Methods, and the MHC restriction specificity and the phenotype of Iat were examined in parallel.

KLH-primed Th cells of B6C3F$_1$ → B6 or B6C3F$_1$ → C3H chimera were treated with anti-Iat^k + C, and then were cultured with TNP-primed B10 or B10.BR B cells, respectively (Table II). The cytotoxic treatment with either anti-H-2^k or anti-H-2^b completely eliminated the helper function of T cells of both F_1 → B6 and F_1 → C3H chimera, indicating that the functioning helper T cells are of the F_1 bone marrow origin. These chimeric T cells are capable of helping only the host type B cells but not those of the other partner haplotype.

As shown in Table II, the treatment of KLH-primed T cells of F_1 → C3H chimera with the two anti-Iat mAb, 2L2 and 74L, abrogated the H-2^k-restricted helper activity, whereas the H-2^b-restricted Th activity of F_1 → B6 chimera was unaffected by the same treatment. Since these two types of chimeric T cells, having the identical F_1 genotype but different H-2 restriction specificities, showed discrete sensitivity to the anti-Iat^k, the Iat epitopes associated with one MHC restriction should be mutually exclusive in F_1 T cells matured under the different thymic environment.

To ask whether anti-Iat^k are selectively acting on the I-A^k-restricted or on I-E^k-restricted response, KLH-primed Th cells of (B10 × B10.A)F_1 → B10, F_1 → 3R, F_1 → 4R, and F_1 → B10.A chimeras were treated with anti-Iat^k + C. Th cells of the former two chimeras are I-A^b-restricted and can cooperate with H-2^b B cells. Th cells of the latter two chimeras are H-2^k-restricted, while the restriction specificity of the F_1 → 4R chimera is confined to the I-A^k subregion. The treated cells were cocultured with TNP-primed B10 or B10.A B cells, and

TABLE III
Expression of Iat^k on I-A^k-restricted Th Cells

Th cells treated with:	IgG anti-TNP PFC/culture			
	B10 B cells		B10.A B cells	
	$F_1 \rightarrow$ B10 Th	$F_1 \rightarrow$ 3R Th	$F_1 \rightarrow$ 4R Th	$F_1 \rightarrow$ B10.A Th
C alone	2,640 ± 47	1,625 ± 134	1,693 ± 83	1,940 ± 24
1L9 + C	2,531 ± 97	1,567 ± 48	1,536 ± 35	1,835 ± 119
2L2 + C	2,838 ± 89	1,631 ± 91	983 ± 35	785 ± 20
GK1.5 + C	47 ± 4	20 ± 4	24 ± 6	47 ± 8

10^6 KLH-primed Th cells of $F_1 \rightarrow$ B10, $F_1 \rightarrow$ 3R, $F_1 \rightarrow$ 4R, and $F_1 \rightarrow$ B10.A chimera origin were treated with indicated antibody + C. The residual cells were cocultured with 3×10^6 TNP-primed B10 or B10.A B cells in the presence of 1 ng/ml TNP-KLH. B cells alone gave no PFC. The chimera Th cells provided no help to nonrecipient I-A-type parental B cells.

TABLE IV
Adaptive Expression of Iat^k on T Cells of Parent $\rightarrow$ F_1 Chimera

Th cells treated with:	IgG anti-TNP PFC/culture	
	B10 B cells + B6 $\rightarrow$ F_1 Th cells	B10.BR B cells + B6 $\rightarrow$ F_1 Th cells
C alone	1,843 ± 79	696 ± 52
Anti-H-2^k + C	1,791 ± 259	627 ± 32
Anti-H-2^b + C	0	0
1L9 + C	1,664 ± 257	869 ± 105
2L2 + C	1,971 ± 348	153 ± 77
74L + C	1,536 ± 331	140 ± 77

10^6 KLH-pulsed B6C3 F_1 Acc-primed Th cells of B6 $\rightarrow$ B6C3 F_1 chimera origin were treated with indicated antibody + C. The residual cells were cocultured with 3×10^6 TNP-primed B10 or B10.BR B cells in the presence of 1 ng/ml TNP-KLH. B cells alone gave no PFC.

the effect of anti-Iat^k on these I subregion–restricted Th cells was assessed. The results shown in Table III demonstrate that the treatment of KLH-primed Th cells of $F_1 \rightarrow$ 4R and $F_1 \rightarrow$ B10.A chimera with anti-Iat^k mAb abrogated the helper activity, while none of the antibodies were able to affect Th of both $F_1 \rightarrow$ B10 and $F_1 \rightarrow$ 3R chimeras. The results indicate that the I-A^k-restricted Th activity can be affected by anti-Iat^k.

Iat Epitopes Are Adaptively Induced by Chimeric Host Environment on T Cells in Association with Acquisition of a New MHC Restriction Specificity. To examine whether the H-2^b bone marrow stem cells would become Iat^k-positive by an adaptive process in the parent $\rightarrow$ F_1 chimera, where T cells acquire the H-2^k-restriction specificity, B6 $\rightarrow$ F_1 chimeras were primed intraperitoneally with KLH-pulsed F_1 Acc cells. Th cells of such chimeras were treated with anti-Iat^k + C, and the residual activity to help TNP-primed B10 or B10.BR B cells was studied (Table IV). The successful reconstitution of T cells by the transplantation of H-2^b bone marrow cells was confirmed by the abrogation of Th cell activity by the treatment with anti-H-2^b but not with anti-H-2^k antibodies. None of the anti-Iat mAb could eliminate helper activity for B10 B cells. The two mAb, 2L2

TABLE V

Adaptive Expression of Iat^k on T Cells of Fully Allogeneic Chimera

Th cells treated with:	IgG anti-TNP PFC/culture	
	B10 B cells + C3H → B6 Th cell	B10.BR B cells + B6 → C3H Th cell
C alone	899 ± 87	511 ± 82
Anti-K^k + C	0	579 ± 150
1L9 + C	849 ± 55	647 ± 33
2L2 + C	882 ± 81	7 ± 7
74L + C	798 ± 21	32 ± 32

10^6 KLH-pulsed B6C3 F_1 Acc-primed Th cells of C3H → B6 or B6 → C3H chimera origin were treated with indicated antibody + C. The residual cells were cocultured with 3×10^6 TNP-primed B10 or B10.BR B cells in the presence of 1 ng/ml TNP-KLH. B cells alone gave no PFC. C3H → B6 Th cells provided 25 PFC to B10.BR B cells and B6 → C3H Th cells provided no PFC to B10 B cells.

and 74L, selectively eliminated chimeric T cells that collaborate with B10.BR B cells. The results indicate that T cells of H-2^b genotype expressed Iat^k epitopes when differentiated in the F_1 environment. It was also noted that only those that acquired the H-2^k restriction specificity were Iat^k-positive.

The adaptive nature of Iat epitopes was confirmed by the expression in the fully allogeneic chimeras. C3H → B6 and B6 → C3H chimeric mice were primed with KLH-pulsed F_1 Acc cells. The primed T cell fraction was treated with anti-Iat^k + C and was tested for their acquired ability to help the TNP-primed B10 (H-2^b) or B10.BR (H-2^k) B cells (Table V). The treatment of T cells of C3H → B6 chimeras with any of the anti-Iat^k mAb was unable to affect their helper function. In contrast, the helper activity of KLH-primed T cells of B6 → C3H chimera, which collaborate only with H-2^k (B10.BR) B cells, was completely eliminated by the treatment with anti-Iat^k + C. Since T cells of the H-2^b haplotype do not generally express Iat^k epitopes, the results indicate that the Iat^k epitopes are adaptively acquired by Th cells differentiated under the influence of environmental H-2.

Discussion

In the present experiment, the Iat epitopes[2] that had been determined to be associated with the MHC restriction site of T cell receptor were found to undergo systematic alterations in the bone marrow chimera according to the environmental MHC where T cells acquire a new MHC restriction specificity. This was determined with a series of anti-Iat mAb produced by the combination of I region–incompatible mouse strains (A.TL and A.TH), but were selected for their exclusive reactivity with mature functional T cells (10). This is so far the first demonstration of the alteration of epitopes associated with T cell receptors according to the adaptive changes of MHC restriction specificity.

The adaptive changes in the MHC restriction on Th cells in radiation bone marrow chimeras have been well documented by a number of authors (13–17). In general, such alterations are determined in the thymus by environmental class II polymorphism, by which T cells are selected to recognize the restriction

elements on antigen-presenting cells and B cells in the antigen cognitive and interacting performances. None of the previous experiments were, however, able to show somatic alterations in the epitopes on MHC-restricted T cells of chimeric mice. The present results finally proved the notion that Iat epitopes are not present on the direct products of I region genes (class II molecules) but are associated with the structure somatically acquired by T cells through the selection by class II antigens during the differentiation. Such structures are used as the MHC restricting elements and are used in the antigen recognition and cell interactions. The blocking of cell interactions by anti-Iat mAb indicate that the epitopes are directly associated with the MHC restriction sites on T cells.[2] It has been demonstrated (26) that the pattern of Iat epitopes expressed on alloreactive T cells against H-2^s stimulator is partly influenced by non–H-2-linked genes possessed by bone marrow stem cells. However, in the present experimental system dealing with the self-MHC–restricted Th, there was no difference in the expressions of Iat epitopes on Th cells according to the origin of stem cells. For example, the pattern of inhibition by anti-Iat of the Th cell function was identical between C3H and B10.BR, which made it impossible to examine the influence of genomic materials of stem cells on the Iat epitope pattern of chimeric Th cells. Such differences in the inhibitory effect of anti-Iat on different T cell functions probably reflects the unequal expressions of Iat epitopes on alloreactive T cells and self-MHC–restricted Th cells.

The treatment of heterogeneous Th cell population from normal mice with a given single monoclonal anti-Iat antibody could eliminate the majority of Th activity, even though the effect was always less than that with anti-L3T4a antibody. This inhibition has been shown not due to the induction of Ts cells.[2] The results indicate that the expression of Iat epitopes are overlapped on populations of several H-2^k-restricted Th cell clones. Since the restriction epitopes (histotopes) on class II antigen are limited (23), the T cell receptors recognizing these epitopes should have limited heterogeneities, as we see the prevalent usage of any single Iat^k epitopes by H-2^k-restricted Th populations. This is clearly different from usual T cell idiotopes, which are expressed only on limited clones with given antigen specificities. Thus, it appears that Iat epitopes are associated with the common prototypic structure for the MHC-restricted but not antigen-specific cell interactions.

The significance of Iat epitopes in the cell interactions and recognition has been supported by several other experiments. The presence of Iat epitopes on antigen-specific and MHC-restricted augmenting T cell factor was the first observation to indicate that the Iat-bearing molecules mediate the regulatory cell interactions (19, 24, 25). Anti-Iat have been shown to inhibit autologous and allogeneic mixed lymphocyte reaction by blocking the responder T cells but not stimulators (26). The in vivo administration of an anti-Iat^k was found (12) to be inhibitory for the H-2^k-restricted helper T cell activity. We have recently observed that anti-Iat^k are able to induce polyclonal proliferative response of a fraction of normal unprimed T cells of H-2^k mice (Yagi, J., Y. Asano, and T. Tada, manuscript in preparation). These results indicate that Iat epitopes are associated in the actual H-2 restriction and allorecognition site of T cell receptors,

although the pattern of the expression of epitopes may differ from one functional T cell to the other.

The molecular nature of the Iat-bearing receptor is not known. We have not yet been able to precipitate the molecules comparable to the TcR $\alpha\beta$ heterodimer with any of anti-Iat mAb by this time. One of the anti-Iat mAb was shown to precipitate a 33 kD polypeptide from an augmenting T cell hybridoma (11), which does not correspond to either TcR or MHC class II polypeptides. By the combination of hetero- and alloantibodies against TcR and T cell clones expressing high amounts of Iat, we are now performing comparative biochemical studies of TcR and Iat-bearing molecules. Further studies using these anti-Iat antibodies may provide us the information concerning the composition of T cell receptors for MHC-restriction and the mechanisms of diversification of T cell repertoire.

Summary

We described in this paper systematic alterations in the expression of unique I region controlled epitopes on helper T cells (Th) in chimeras according to the changes in their H-2 restriction specificity. Taking advantage of the reactivity of monoclonal antibodies (anti-Iat) putatively specific for the epitopes indirectly controlled by I region and expressed in association with the Ia^k restriction site of Th, we examined the alterations of these epitopes on Th cells from various bone marrow chimeras. Iat^k epitopes were physiologically expressed on Ia^k-restricted but not on Ia^b-restricted Th cells in $(H\text{-}2^k \times H\text{-}2^b)F_1$ mice. In the chimeric condition, the $H\text{-}2^k$-restricted Th of B6 $\rightarrow$ F_1 chimera acquired the expression of Iat^k even though B6 Th is unable to express Iat^k when developed under the physiologic condition. Iat^k are also found on Th of fully allogeneic chimera of B6 $\rightarrow$ C3H, whereas Th cells of C3H $\rightarrow$ B6 completely lost the Iat^k expression. These results indicate that Iat epitopes originally defined as unique I region–controlled determinants selectively expressed on T cells are not encoded by the I region genes but are associated with the T cell receptor that sees the self Ia. The epitopes undergo the adaptive alterations according to the acquisition of a new MHC restriction. This is the first example to demonstrate the epitope associated with T cell receptor which undergo the systematic adaptive differentiation.

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