

## ORIGIN AND SPECIFICITY OF AUTOREACTIVE T CELLS IN ANTIGEN-INDUCED POPULATIONS

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Autoreactive T cells are induced at relatively high frequency in antigen-stimulated populations of lymph node cells (1, 2). Cloned lines of such T cells have been selected *in vitro* and were shown (2) to be activated in the absence of any identifiable foreign antigen by major histocompatibility complex (MHC)<sup>1</sup>-syngeneic but not MHC-allogeneic stimulators. These autoreactive T cells provide a nonspecific helper function that serves to enhance proliferation and maturation to Ig secretion of B cells activated through carrier-specific signals, or by a T-independent antigen (2).

Efficient selection of autoreactive T cells from primed populations *in vitro* is dependent upon secondary stimulation with antigen during initial culture (1, 2). This suggests an interaction, directly or indirectly, between antigen-specific T cells and precursors to autoreactive T cells. The induction of autoreactive T cells may require activation of autologous stimulators through an antigen-mediated interaction with specific T cells. Autoreactive T cells might also derive from some antigen-specific clones that express a relatively high-affinity receptor for self. After activation, such clones may, through mutation or increased representation of membrane receptors, achieve a higher functional avidity for MHC determinants and become antigen-independent. These possibilities are not mutually exclusive.

To further investigate the relationship between antigen-specific and autoreactive T cells, we have characterized the MHC specificity of autoreactive T cell clones from diverse donors after immunization with different antigens. We report here that the MHC fine specificity of autoreactive T cells for unique F<sub>1</sub> hybrid determinants of BALB.K × BALB.B F<sub>1</sub>, and for mutant I-A<sup>b</sup> determinants of the B6.C-H-2<sup>bm12</sup> (bm12) strain is similar to that described previously (4, 5) for antigen-specific T cells. We demonstrate, furthermore, that in the absence of an exogenous source of T cell factors, the predominant MHC specificity of autoreactive T cell clones selected from an antigen-primed population reflects the predominant MHC restriction specificity of antigen-specific T cells in that

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<sup>1</sup> *Abbreviations used in this paper:* B<sub>DNP</sub>, anti-Thy-1.2, anti-Lyt-2.2, and complement-treated spleen cells from DNP-ovalbumin-primed donors; Con A, concanavalin A; CTLL-2, IL-2-dependent cytotoxic T lymphocyte line; DNP, dinitrophenyl; F<sub>0</sub>, fraction of limiting dilution cultures in which no functional activity is detected; GLΦ, terpolymer of glutamic acid, lysine, and phenylalanine; IL-2, interleukin 2; KLH, keyhole limpet hemocyanin; MHC, major histocompatibility complex; SMLR, syngeneic mixed lymphocyte response.

population. Thus, I-E subregion-specific autoreactive T cells are detected at a much higher frequency after immunization with the I-E-restricted antigen polyglutamic acid-lysine-phenylalanine (GL $\Phi$ ) than with the predominantly I-A restricted antigen, keyhole limpet hemocyanin (KLH). This suggests that many autoreactive T cells selected under these conditions derive from antigen-specific, MHC-restricted precursors. As further discussed below, autoreactive T cells selected in the presence of concanavalin A (Con A)-induced supernatant factors appear, in contrast, to be recruited from a larger independent pool of predominantly I-A-specific precursors.

### Materials and Methods

*Mice.* The H-2 congenic strains, BALB.B (H-2<sup>b</sup>), BALB.K (H-2<sup>k</sup>), and F<sub>1</sub> hybrids were bred at Columbia University, New York, from breeding pairs provided by Dr. Frank Lilly of the Albert Einstein College of Medicine, New York. Breeding pairs of C57BL/6 and the I-A<sup>b</sup> mutant B6.C-H-2<sup>bm12</sup> were provided by Dr. Roger Melvold, Northwestern University Medical School, Chicago, IL. CBA/N were purchased from Dominion Laboratories, Dublin, VA. BALB/cByJ, C57BL/10, B10.A(5R), and NZB were purchased from The Jackson Laboratories, Bar Harbor, ME.

*Antigens.* KLH was purchased as an ammonium sulfate slurry from Calbiochem-Behring Corp., San Diego, CA. GL $\Phi$ -8 was the generous gift of Dr. Ronald Schwartz, National Institutes of Health, Bethesda, MD.

*T Cells.* Mice were immunized subcutaneously at the base of the tail with 100  $\mu$ g of KLH or 125  $\mu$ g of GL $\Phi$  emulsified in complete Freund's adjuvant in a total volume of 50  $\mu$ l. 4 (for KLH) or 7 (for GL $\Phi$ ) d later, the inguinal and paraaortic lymph nodes were removed, and teased through a stainless steel mesh into Hank's balanced salt solution. Where indicated, lymph node cell suspensions were passaged over nylon wool (3.0 denier, type 200, DuPont Co., Wilmington, DE). Limiting-dilution cultures were initiated directly from primed lymph node cell suspensions in 100  $\mu$ l RPMI 1640 medium supplemented with 10 mM (final) Hepes, 1 mM L-glutamine, 50 U/ml penicillin, 50  $\mu$ g/ml streptomycin,  $5 \times 10^{-5}$  M 2-mercaptoethanol, and 10% FCS (complete medium). Incubation was at 37°C in a humidified incubator with 7.5% CO<sub>2</sub> in air. Limiting-dilution cultures, in 96-well, round-bottom plates, received between  $2 \times 10^3$  and  $3 \times 10^4$  primed lymph node cells,  $3 \times 10^4$  2,000 rad irradiated syngeneic spleen cells, and either 40  $\mu$ g/ml KLH or 100  $\mu$ g/ml GL $\Phi$ . Except where indicated, complete medium was supplemented with 10% Con A-stimulated rat spleen supernatant and 2 mg/ml (final) methyl- $\alpha$ -D-mannopyranoside for optimal T cell cloning efficiency. Cultures were fed weekly and restimulated every second week with syngeneic spleen cells and antigen to select both specific and autoreactive clones, or with syngeneic spleen cells alone to select autoreactive clones. Clonal specificity was determined from the requirements for induction of interleukin (IL-2) secretion or of nonspecific helper function at least 2 wk after the last stimulation.

*IL-2 Assays.* Culture supernatants were assayed for the ability to support the growth of the IL-2 dependent T cell line CTLL-2 (provided by Dr. Steven Gillis, Immunex Corp., Seattle, WA). CTLL-2 was maintained in complete medium supplemented with 10% Con A supernatant. Assays were performed in duplicate on 50% culture supernatants in 100  $\mu$ l volume, with  $4 \times 10^3$  CTLL-2 harvested 3 d after their last feed. Cell viability was determined after 20 h incubation, using the colorimetric assay described by Mosmann (3). Briefly, 10  $\mu$ l of a 5 mg/ml solution of the tetrazolium salt (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (Sigma Chemical Co., St. Louis, Mo.) was added to each culture well. Incubation was continued at 37°C in a humidified incubator with 7.5% CO<sub>2</sub> in air for 3 h. At the end of this incubation, formazan crystals that were formed through the action of mitochondrial dehydrogenases in the remaining viable cells were dissolved by addition of 100  $\mu$ l of acidified isopropanol (0.04 N HCl). Absorbance at 570 nm was determined in an enzyme-linked immunosorbent assay reader.

*Helper Assays.* Primed B cells were prepared, and secondary in vitro antibody-forming

cell cultures were initiated in 0.1 ml complete medium, as previously described (2). A hemagglutination assay was adapted for large scale screenings of T cell-enhanced DNP-specific antibody secretion in 0.1 ml cultures. Spent culture medium was aspirated away and replaced with 0.1 ml fresh medium including 5% fetal calf serum on day 4. Incubation was continued at 37°C for an additional 24 h, at which time supernatants were harvested. Duplicate aliquots of these supernatants were assayed for specific agglutination of trinitrophenyl-conjugated horse red blood cells in V-shaped wells (Titertek 1-220-25X; Flow Laboratories, McLean VA). Supernatants from multiple control cultures that did not receive T cells were assayed in parallel for T-independent responses. When 10  $\mu$ l supernatant aliquots were transferred, the T-dependent response to dinitrophenyl (DNP)-Ficoll, usually <25 PFC/culture, was not detectable by hemagglutination assay, whereas T cell-enhanced responses, usually >100 PFC/culture, were strongly positive. On occasion it was necessary to reduce the volume of the supernatant aliquots transferred, in order to distinguish T cell-enhanced responses from a larger-than-usual T-independent response. These instances could always be identified by initial titration of control supernatants. It was possible, using this assay, to screen several hundred limiting-dilution cultures for both helper activity and MHC specificity.

## Results

*Equivalent Relative Frequency of Antigen-specific and Autoreactive T Cells in Normal, Autoimmune, and xid Strains.* The relative frequency of precursors to antigen-specific and autoreactive T cells was determined for limiting-dilution clones of lymph node cells from KLH-primed donors. Limiting-dilution cultures in these experiments were initiated with excess irradiated syngeneic spleen cells and antigen, and were maintained in the presence of Con A-induced supernatant factors. Specificity of each clone was determined in functional assays of the requirements for induction of IL-2 secretion, or of the ability to enhance the antibody response to DNP-Ficoll, a type 2 T-independent antigen. Duplicate aliquots of clonal progeny, after 4–6 wk of in vitro expansion, were restimulated with syngeneic or allogeneic spleen cells in the presence or absence of KLH. Clones that could be restimulated in the absence of KLH with syngeneic but not allogeneic spleen cells were scored as autoreactive. In a small fraction of limiting-dilution cultures, functional activity was detected in the presence of either syngeneic or allogeneic spleen cells. It is likely that, for the most part, these are T cells that are in an activated state due to prior in vitro stimulation.

Antigen-specific and autoreactive T cell clones were selected from KLH-primed BALB/c and NZB strains, and either normal female or immune-defective male CBA/N  $\times$  BALB/c F<sub>1</sub> hybrids. Because of variation in the recovery of clones even from donors of the same strain, it is most meaningful to compare relative levels of antigen-specific and autoreactive clones in the different donor populations. The results in Table I show that a substantial proportion of autoreactive T cells were selected from each of these diverse donors.

*Autoreactive and Antigen-specific T Cells Share Specificity for Unique MHC Determinants.* We have previously demonstrated (4) that as many as one third of KLH-specific T cell clones derived from BALB.K  $\times$  BALB.B F<sub>1</sub> hybrids are restricted to unique F<sub>1</sub> hybrid MHC determinants not represented in B cells of either parental type. The results in Table II show that a similar fraction (38%) of BALB.K  $\times$  BALB.B F<sub>1</sub> autoreactive T cell clones are specific for unique F<sub>1</sub> hybrid determinants.

In similar experiments, we determined that autoreactive T cell clones, like

TABLE I  
*Antigen-induced Specific and Autoreactive T Cell Clones in BALB/c, NZB, and xid Donors*

Activation for IL-2 secretion			Phenotype	Number of clones				
Syngeneic stimulators plus KLH	Syngeneic stimulators	Allogeneic stimulators		Exp. 1 BALB/c	Exp. 2 BALB/c	Exp. 3 NZB	Exp. 4 CBA/N × BALB/c F <sub>1</sub>	
							Male	Female
+	-	-	KLH-specific	13	10	8	4	7
+	+	-	Autoreactive	22	13	9	14	13
+	+	+	Activated	5	3	4	0	1

Limiting-dilution clones were selected directly from KLH-primed lymph node cells of the indicated donor strains. Both antigen-specific and autoreactive precursors were limiting when between  $5 \times 10^3$  and  $15 \times 10^3$  primed lymph node cells were seeded in individual wells. Using Poisson analysis (4) we determined that the mean precursor frequency under these conditions was  $<0.7$  cells/well. Clonal specificity was tested with both syngeneic BALB/c (Exp. 1, 2, 4) or NZB (Exp. 3) and allogeneic BALB.B (Exp. 1-4) stimulators. Supernatants of test cultures were harvested at 72 h for IL-2 assay. The table indicates the major patterns of response observed.

TABLE II  
*BALB.K × BALB.B F<sub>1</sub> Autoreactive T Cell Clones Specific for F<sub>1</sub> Hybrid MHC Determinants*

IL-2 secretion			MHC specificity	Number of autoreactive clones
BALB.K stimulators	BALB.B stimulators	K × B F <sub>1</sub> stimulators		
+	-	+	Parental (H-2 <sup>k</sup> )	14
-	+	+	Parental (H-2 <sup>b</sup> )	15
-	-	+	Unique F <sub>1</sub>	18
			F <sub>0</sub>	0.51

Autoreactive T cell clones were selected directly from KLH-primed BALB.K × BALB.B F<sub>1</sub> lymph node cells. Clones were maintained for several weeks, and IL-2 secretion was assayed in the absence of KLH. Clonal specificity was determined using stimulators of either parental or F<sub>1</sub> origin, as described in Table I. F<sub>0</sub> is the fraction of lymph node cultures in which no inducible autoreactive T cells were detected.

antigen-specific T cells (5), can be specific for unique mutant I-A determinants of the bm12 strain. In the two experiments shown in Table III, the largest group of C57BL/6 × bm12 F<sub>1</sub> autoreactive T cell clones was specific for determinants shared by parent and mutant, a second group was specific for unique mutant determinants, and the few remaining clones appeared to be specific for wild type determinants absent in the mutant.

*Choice of Antigen Can Influence Specificity of Autoreactive T Cells in Antigen-Induced Populations.* The above experiments demonstrate that antigen-specific and autoreactive T cells are not independently regulated in normal, autoimmune, and immune defective (*xid*) strains, and that they share parallel specificities for unique MHC determinants. We considered the possibility that MHC-specific autoreactive T cells might derive from some antigen-specific, MHC-restricted precursors that have, as a result of mutation or maturation, become antigen-independent. If this were the case, it might be predicted that the choice of an I-A- or I-E-restricted antigen would influence the MHC specificity of autoreactive T cells in an antigen-induced population. A major concern in carrying out such

TABLE III  
*B/6 × bm12 F<sub>1</sub> Autoreactive Helper T Cell Clones Specific for Mutant I-A Determinants*

Specific antibody secretion		MHC specificity	Number of autoreactive clones	
bm12 B <sub>DNP</sub> + DNP-Fi-coll	B10 B <sub>DNP</sub> + DNP-Ficoll		Exp. 1	Exp. 2
+	-	Mutant only	44	31
-	+	Wild type only	2	3
+	+	Shared F <sub>0</sub>	51	37
			0.16	0.41

Autoreactive T cell clones were selected directly from KLH-primed B/6 × bm12 F<sub>1</sub> lymph node cells. The ability to enhance the DNP-specific response to DNP-Ficoll was assayed with B<sub>DNP</sub> spleen cells that had been primed with DNP-ovalbumin, treated with anti-Thy-1.2, anti-Lyt-2.2, and complement, and were of either bm12, B10, or B10.A(4R) origin, as described in Materials and Methods. Clones that enhanced both bm12 and B10 responses were specific for MHC determinants shared by mutant and wild type, as they did not enhance responses of allogeneic B10.A(4R).

TABLE IV  
*I-region Specificity of Autoreactive T Cell Clones*

IL-2 secretion		I-region specificity	Number of autoreactive clones	
B10 stimulators	B10.A(5R) stimulators		GL $\phi$ primed	KLH primed
+	+	I-A	12	36
-	+	I-E	13	2

Autoreactive T cell clones were selected from nylon wool-passaged B10.A(5R) lymph node cells primed with either GL $\phi$  or KLH. Cultures were restimulated with the immunogen at initiation and on day 14, and were maintained in the absence of Con A-induced supernatant factors. Cloning efficiency for autoreactive T cells is substantially reduced under these conditions. Clones induced to IL-2 secretion by both B10 and B10.A(5R) stimulators were not induced by allogeneic B10.A(4R) stimulators.

an experiment, however, is the possibility that a relatively stable pool of autoreactive precursors exists, and can be recruited into any on-going immune response (see below). T cells in such a pool might derive from previous antigenic stimulation, or might be of independent origin. In either case, they would tend to obscure the influence of the current immunogen on autoreactive MHC-specificity. In order, therefore, to reduce the likelihood of recruitment from such a pool, these particular experiments were carried out in the absence of any exogenous source of T cell factors. As shown in Table IV, under these conditions, only 2 of 38 autoreactive T cell clones that were derived following stimulation with the predominantly I-A-restricted antigen, KLH (6), were I-E-specific. In contrast, 13 of 25 autoreactive clones derived after stimulation with the I-E-restricted antigen, GL $\Phi$ , were I-E-specific. The difference in proportions is highly significant ( $P < 0.001$ ).

### Discussion

Autoreactive T cells are highly represented in antigen-induced populations of lymph node cells. Our present experiments explore the relationship between autoreactive and antigen-specific T cells. We have selected autoreactive T cell clones that are specific for unique F<sub>1</sub> hybrid MHC determinants or for the mutant I-A determinants of the bm12 strain. These results suggest that autoreactive T cells recognize MHC determinants similar to those that serve as restriction elements for antigen-specific helper cells (4, 5).

We have suggested several possible interpretations of our previous observation (1, 2) that antigen stimulation greatly facilitates the selection of murine autoreactive T cell clones *in vitro*. Activation of Ia<sup>+</sup> stimulators through an antigen-mediated interaction may be required for recruitment of autoreactive precursors. We have recently found that a Con A-stimulated rat spleen supernatant, which induces high-level Ia expression in some tumor lines, can replace the requirement for initial restimulation with antigen in the efficient selection of autoreactive T cell clones from primed lymph node cells. This contrasts with other IL-2-containing supernatants that do not suffice for this purpose. Clayberger et al (7) have recently described an autoreactive T cell clone whose activation in normal mouse serum requires mitogen-stimulated syngeneic spleen cells. It may well be, as suggested by these workers, that *in vivo* expansion of autoreactive precursors is regulated, at least in part, by the availability of activated stimulators.

Antigen-specific T cells may, in addition, contribute directly to generation of a pool of autoreactive precursors. Several reports (8, 9) have described autoreactive T cell hybridomas that are induced to IL-2 secretion by MHC-syngeneic stimulators alone, but whose secretion is further augmented in the presence of specific antigen. It is possible that some autoreactive T cells derive from antigen-specific clones that express a relatively high-affinity receptor for self MHC. We demonstrate here that the specificity of autoreactive T cell clones selected from primed populations grown in the absence of Con A-stimulated supernatant factors reflects the predominant MHC restriction specificity of T cells specific for the immunogen. Thus, I-E subregion-specific autoreactive T cells are detected at a much higher frequency after immunization with the I-E-restricted antigen GL $\Phi$  than with the predominantly I-A-restricted antigen KLH (6). These experiments strongly suggest that some autoreactive T cells derive from antigen-stimulated precursors. Further experiments of our own and others (R. Hodes, personal communication) indicate, in contrast, that when autoreactive T cell clones are selected from antigen-stimulated populations in bulk cultures and/or in the presence of Con A-stimulated supernatant factors, the predominant specificity is for the I-A subregion, and is independent of the choice of I-A- or I-E-restricted antigens. This suggests that, under these conditions, many autoreactive T cells are recruited from an independent pool of predominantly I-A-specific precursors. Since autoreactive T cell clones are selected with far greater efficiency in bulk cultures (1), or in the presence of exogenous T cell factors, the contribution of autoreactive T cells from this pool is large compared to the number of autoreactive T cells derived directly from antigen-stimulated precursors. It is likely that limited recruitment from this pool, even in the absence of exogenous T cell factors, accounts for those I-A-specific clones induced after

immunization with GL $\Phi$ . It remains to be determined whether the autoreactive precursors in this pool are themselves derived from previous antigenic stimulation, or from other sources.

Autoreactive T cells in antigen-induced populations may include those T cells that are stimulated in syngeneic mixed lymphocyte responses (SMLR) (10–12). Glimcher et al (13) have reported that effective induction of murine SMLR requires an enriched population of stimulators. This might be achieved by activation of Ia<sup>+</sup> cells in the course of an antigen-specific response. Our observation that the relative frequency of antigen-induced autoreactive T cells remains high in NZB mice (Table I) could be reconciled with previous reports (14–16) of SMLR deficiency in aged NZB if specific antigen-stimulation compensates for some defect in NZB. Evidence that T cells of aged NZB can be recruited in SMLR initiated by nondeficient young NZB has been described (16).

In diverse strains, following immunization with different antigens, autoreactive T cells are induced at a greater frequency than antigen-specific T cells. We have previously demonstrated (1, 2) that these autoreactive T cells have a nonspecific helper function. This has suggested that the physiological significance of such T cells, both in vivo and in vitro, is to enhance immune responses under conditions in which carrier-specific helper T cells are limiting. In the absence of a mechanism for antigen-focused interaction with hapten-specific B cells, autoreactive T cells do not participate efficiently in MHC-restricted induction of specific responses. This limitation in their function, as compared to carrier-specific T cells, can be entirely attributed to their different specificities, and need not imply any other difference in intrinsic properties. Finnegan et al (17) have recently described direct MHC-restricted activation by excess autoreactive T cells of some hapten-specific precursors in a primed population. It is possible that these B cells were in an activated state in which increased Ia expression (18) permitted a focused interaction with autoreactive T cells. This class of B cells was either absent in our experiments with hyperimmune donors, or could not be detected above the background of MHC-unrestricted response. In any case, quantitative analysis of B cell activation induced by carrier-specific and autoreactive helper T cell clones demonstrates that induction of the majority of hapten-specific precursors in primed B cell populations requires carrier-specific help (2).

### Summary

We have characterized the major histocompatibility complex (MHC) specificity of autoreactive T cell clones arising from diverse donors after immunization with different antigens. The MHC fine specificity of autoreactive T cells for unique F<sub>1</sub> hybrid determinants of BALB.K  $\times$  BALB.B F<sub>1</sub>, and for the mutant I-A<sup>b</sup> determinants of the B6.C-H-2<sup>bm12</sup> (bm12) strain is similar to that previously described (4, 5) for antigen-specific T cells. We find, furthermore, that the MHC specificity of autoreactive T cell clones selected from primed populations grown in the absence of Con A-stimulated supernatant factors reflects the predominant MHC restriction specificity of T cells specific for the immunogen. Thus, I-E subregion-specific autoreactive T cells are detected at a much higher frequency after immunization with the I-E-restricted antigen, GL $\Phi$  (terpolymer of glutamic acid, lysine, and phenylalanine), than with the predominantly I-A-restricted

antigen, keyhole limpet hemocyanin (KLH). These experiments strongly suggest that some autoreactive T cells are derived from antigen-stimulated precursors. This result contrasts with that obtained when autoreactive T cells are selected in bulk cultures, or in the presence of exogenous T cell factors. We conclude that, under optimal conditions, most autoreactive T cells are recruited from a relatively stable pool of predominantly I-A-specific precursors. Autoreactive precursors in this pool might themselves derive from previous antigenic stimulation, or be of independent origin.

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