THE BIOLOGIC SIGNIFICANCE OF ALLOREACTIVITY
The Ontogeny of T-Cell Sets Specific
for Alloantigens or Modified Self Antigens*

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T-lymphocyte populations comprise functionally different cell subsets which carry distinctive Ly surface components (1). The contribution of these T-cell subsets to the cytotoxic T-lymphocyte (CTL)1 response against alloantigens has been extensively studied. In adult life, T cells which express the Thy 1+ Ly1-2+3+ surface phenotype (Ly23 cells) bind and react to foreign H-2K/D region products (2, 3) and are responsible for alloreactive prekiller and killer-effector activity. The generation of cytotoxicity by limiting numbers of Ly23 prekiller cells is amplified by cells of the Ly1 set, which are selectively stimulated by products of the I region of the major histocompatibility complex (MHC) (4).

The frequency of prekiller cells in the Ly23 population capable of developing into cytotoxic effector cells after stimulation across a single MHC haplotype difference has been estimated at approximately 1-3% (5-7). This inordinately large proportion of alloreactive prekiller cells is in accord with the high frequency of cells that mount a proliferative response after stimulation by cells differing at a single MHC haplotype (8). Taken together these observations imply the presence of an extraordinarily large number of alloreactive cells in the T-cell population (9). This apparent commitment of T cells to specificites expressed by polymorphic variants of the MHC (alloreactivity) has puzzled immunologists, because of the apparent biologic irrelevance of immunity to foreign MHC products. One explanation for this high level of alloreactive cells and for the strong allogeneic response elicited without prior in vivo priming is based upon the recent evidence that T cells may recognize foreign antigens in association with autologous MHC gene products on the surface of cells (10). Alloreactivity, may thus reflect a high degree of cross-reactivity of T-cell receptors for autologous MHC products associated with antigen, and polymorphic variants of MHC gene products within the species (alloantigens) (11, 12). According to this view alloreactive T memory cells may be continuously generated after stimulation by autologous MHC...
products associated with antigen, such as a virus. This view is consistent with earlier findings that alloreactive CTL specifically lyse autologous cells coupled with trinitrophenyl (TNP) molecules (11).

One approach to this question involves a comparative analysis of the cellular basis for the CTL response after stimulation by modified autologous MHC products or allogeneic MHC products. Preliminary experiments have indicated that cells bearing the Ly123 phenotype (which arise earliest in ontogeny [3]) give rise to Ly23 cytotoxic cells after stimulation in vitro by chemically modified autologous cells (13), whereas cells of the Ly23 set respond to alloantigens (3). These findings raise the following question: does continuous in vivo stimulation of clones of Ly123 cells by autologous MHC products that have been modified in vivo (by viruses or other agents) result in the formation of the Ly23 memory pool, which can be restimulated by polymorphic variants of MHC antigens?

The experiments reported here and elsewhere (18) indicate that alloreactivity (as manifest in the CTL response) may result from continuous in vivo stimulation of Ly123 cells reactive to autologous cells that appear foreign because they have been modified by association with non-MHC antigens (such as virus); such stimulation results in the generation of Ly23+ memory progeny which specifically lyse cells bearing MHC products that are foreign by virtue of genetic polymorphisms (alloantigens).

Materials and Methods

Mice. 6- to 12-week-old male or female mice of the following strains: C57BL/6 (H-2b), DBA/2 (H-2d), and B10.D2 (H-2d) were purchased from The Jackson Laboratory, Bar Harbor, Maine. B6D2F1 (H-2b/d) mice were purchased from Cumberland View Farms (Clinton, Tenn.). Young B6 mice were bred at Harvard Medical School, Boston, Mass., by Dr. Charles Sidman. B6-Ly2.1 congenic mice were bred at the Sloan Kettering Institute, New York, by Dr. E. A. Boyse.

Tumors. P815 (H-2a) mastocytoma was maintained in DBA/2 mice and the EL4 (H-2b) leukemia was maintained in B6 mice. These tumors were carried in ascites form by weekly intraperitoneal transfer.

Antisera. For details of the preparation and use of antisera to Ly1,2, Ly2,2, and Ly3,2, see Shen et al. (14).

Isolation of Ly+ T-Cell Sets. Before in vitro stimulation, 20-50 × 10^6/ml normal lymph node (LN) cells or spleen cells were incubated with Ly1.2 antiserum, or Ly2.2 plus 3.2 antiserum, or normal mouse serum (NMS) at a final dilution of 1:40 to 1:60 in balanced salt solution supplemented with 10% fetal bovine serum for 40 min at room temperature. After washing once, the cells were resuspended in 1 ml of freshly thawed selected rabbit serum (diluted 1:10 to 1:20 in phosphate-buffered saline) as a source of complement (C), and were incubated for an additional 30 min at 37°C.

After in vitro stimulation, effector (CTL), LN, or spleen cells were incubated with Ly sera + C as stipulated above; this procedure was repeated to ensure optimal specific lysis, as described previously (15).

Generation of CTL. 5 × 10^6 lymph node or spleen cells were incubated at 37°C with 5 × 10^6 irradiated (1,200 rads, General Electric Maximizer 250-III, General Electric Co., Wilmington, Mass.) allogeneic or TNP-modified syngeneic spleen cells in 2 ml × 5 days in 16-mm tissue culture wells (Linbro Chemical Co., New Haven, Conn.) in a humidified atmosphere of 95% air and 5% CO2. Cell culture medium consisted of RPMI-1640, penicillin (100 U/ml), streptomycin (100 μg/ml) supplemented with 2 mM glutamine, 5 × 10^-6 M 2-mercaptoethanol and 10% heat-inactivated fetal calf serum (Microbiological Associates, Walkersville, Md.). Erythrocytes were removed from stimulator cells by a 0.5-min incubation in Tris-HCl/ammonium chloride.

CTL were induced to Sendai virus-modified autologous cells using a protocol similar to
### Table I

| Exp. Stimulator | Target | E:T | Unselected | Ly1 | Ly23 | Ly1 + Ly23 |
|-----------------|--------|-----|------------|-----|------|------------|
| I \(1\) | P815 \(H-2^d\) | \(2.5:1\) | 21§ | 9 | 51 | 25 |
| | EL-4-TNP \(H-2^d\) | 50:1 | 35 | 9 | 62 | 27 |
| II | P815 | 10:1 | 34 | 0 | 51 | 39 |
| | EL-4-TNP | 40:1 | 49 | 0 | 53 | 23 |

*5 × 10⁶ B6 cells of the indicated T-cell set were stimulated with allogeneic DBA/2 \(H-2^a\) spleen cells; Ly1 cells were obtained after treatment of B6 LN cells with Ly2.2 and Ly3.2 antisera + C; and Ly23 cells were obtained after treatment of B6 LN cells with Ly1.2 antisera + C. Ly1 + Ly23 cells represent 1:1 mixtures of the two cell populations. See Materials and Methods for details of treatment and culture conditions.

§ Values are percent specific release of \(^{32}\)Cr against the indicated target cell. Spontaneous release of P815 ranged between 10 and 12%, and EL-4-TNP ranged between 11 and 32%. Minimal lysis of EL-4 target cells was noted.

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Schrader and Edelman (16): 7 × 10⁶ spleen cells were cocultured with 6 × 10⁶ X-irradiated stimulator spleen cells that had been incubated with \(\beta\)-propriolactone-inactivated Sendai virus (Connaught Laboratories, Willowdale, Ontario). Stimulator cells were prepared by incubating 50 × 10⁶ X-irradiated spleen cells and 0.01 ml of \(\beta\)-propriolactone-inactivated Sendai virus in 2 ml of Eagle's minimal essential medium (MEM)-10% fetal calf serum (FCS) for 90 min at 37°C. These cells were washed three times before use.

**Assay of CTL.** The \(^{32}\)Cr release assay has been described in detail (17). Briefly, targets were labeled by incubation with Na \(^{32}\)CrO₄. Lipopolysaccharide (LPS)-stimulated spleen cells (>90% blast cells) were used as a source of target cells as described previously (11). Sendai virus modified target cells were prepared by incubation of 3 × 10⁶ \(^{51}\)Cr-labeled LPS-stimulated spleen cells with 0.01 ml \(\beta\)-propriolactone-inactivated Sendai virus in 2 ml MEM-10% FCS for 90 min at 37°C. These cells were washed three times before use.

0.1 ml of a cell suspension containing \(^{51}\)Cr labeled targets in supplemented MEM (17) was added to 10 × 75 mm round bottom glass tubes containing 0.1 ml of varying numbers of effector cells or normal cells. These cultures were incubated for 4 h at 37°C in 83% N₂, 10% CO₂, and 7% O₂ on a rocking platform. 1 ml of phosphate-buffered saline was added to each tube before centrifugation; supernates were removed and assayed to determine isotope release. All measurements were performed in duplicate or triplicate and the standard error of the mean was always <2-3%. Percent specific release was calculated as \((E-C)/FT-C) × 100\%\), where \(E\) is isotope release from tubes containing immune effectors plus targets, C = isotope release from tubes containing normal spleen cells plus targets (spontaneous release) and FT = maximum isotope release determined after four cycles of freezing and thawing target cells.

**Notations.** Unless otherwise indicated, Ly1 cells signifies cells treated with anti-Ly2.2 + anti-Ly3.2 + C; Ly23 cells signifies cells treated with anti-Ly1.2 + C; and unselected T cells signifies cells treated with NMS + C, according to the protocols stipulated above. For brevity, whenever pretreatment of a cell population is referred to, it is implied that this took place in the presence of complement.

### Results

**T-Cell Sets Responsible for Generation of Alloreactive and Cross-reactive CTL after Stimulation by Allogeneic Cells (Table I).** The in vitro (4) and in vivo\(^2\) generation of Ly23 CTL requires Ly1 help. However, stimulation of large numbers of Ly23 cells in the absence of Ly1 cells results in efficient generation of Ly23\(^*\) CTL, if selected lots of fetal calf sera are used.

\(^{2}\) B. Huber, and H. Cantor. Manuscript submitted for publication.
**Demonstration that Cells of the Ly123 Set are Precursors of Ly23 CTL after Stimulation by TNP-Modified Syngeneic Cells**  

| Donor of responder cell | Pretreatment of responder cells \((+C)\) | T-cell set selected | Sensitization phase: Responder cell populations | Effector phase: % lysis (10:1 E:T) after treatment of MLC-activated cells with: |
|-------------------------|--------------------------------------|---------------------|-----------------------------------------------|--------------------------------------------------|
| A B6                    | NMS                                  | All \((3 \times 10^6)\) | 24                                            | NMS Anti-Ly2.1 Anti-Ly2.2 |
| B B6-Ly2.1,3.2          | Anti-Ly1.2                           | Ly23 \((3 \times 10^6)\) | 0 ND§ ND§ ND§ ND§ | 2 |
| C                       | NMS                                  | A \((3 \times 10^6)\) + B \((3 \times 10^6)\) | 29                                            | 3 |
| D B6-Ly2.1,3.2          | NMS                                  | All \((3 \times 10^6)\) | 19                                            | 4 |
| E B6                    | Anti-Ly1.2                           | Ly23 \((3 \times 10^6)\) | 0 ND§ ND§ ND§ ND§ | 21 |
| F                       | D \((3 \times 10^6)\) + E \((3 \times 10^6)\) | All \((3 \times 10^6)\) | 21                                            | 5 |

* See text for explanation of protocol.  
† Background (spontaneous \(^{51}\)Cr release) was less than 10%.  
§ ND, not done.

Stimulation of B6 (H-2^b^) Ly23 cells with irradiated DBA/2 (H-2^k^) cells in vitro results in the formation of Ly23 progeny that lyse both P815 (H-2^k^) and EL-4-TNP (H-2^b^TNP). Lysis of the latter cells has been shown to be specific, because it is inhibited with cold nonradiolabeled P815 or EL-4-TNP but not EL-4 targets (10). We conclude that activation of Ly23 prekiller cells by allogeneic cells results in the formation of Ly23 CTL that lyse both allogeneic targets as well as chemically modified autologous targets.

**T-Cell Sets Responsible for Generation of CTL after Stimulation by Chemically-Modified Syngeneic Cells** (Table II). B6 cells were stimulated by TNP-coupled syngeneic cells; cytolytic activity was assessed against TNP-coupled syngeneic target cells (EL-4-TNP). Ly123 cells are required for the generation of Ly23 CTL that lyse TNP-coupled syngeneic target cells (13).

The requirement for Ly123 cells indicates that (a) Ly123 cells are precursors of Ly23 killer effector cells or (b) Ly123 cells help Ly23 precursors to differentiate to Ly23 killer-effector cells. The following experiments support the first interpretation: B6 mice (Ly phenotype 1.2, 2.2, 3.2) were used as a source of Ly123 cells (after treatment with NMS); B6-Ly2.1 congenic mice (Ly phenotype 1.2, 2.1, 3.2) were used as the source of Ly23 cells (after treatment with anti-Ly1.2). In a 1:1 mixture of these two preparations any Ly23 killer effector cells that derived from Ly23 prekiller cells would be marked by the Ly2.1 antigen. Cytotoxic effector activity generated by this cell mixture was virtually abolished by treatment with anti-Ly2.2, and completely resistant to treatment with anti-Ly2.1 (Table II). Similar conclusions were drawn from experiments in which cells from B6-Ly2.1 congenic mice were used as the source of Ly123 cells and cells from B6 mice were used as the source of Ly23 cells.

The above findings, taken together, indicate that in adult mice, prekiller activity to TNP-coupled cells and to allogeneic cells reside in different T-cell sets: Ly23 cytotoxic effector cells generated after stimulation by TNP-coupled autologous cells are drawn from the Ly123 precursor pool, while Ly23 cytotoxic effector cells generated after stimulation by allogeneic cells arise almost entirely from Ly23 precursor cells. Ly23*
cytolytic effector cells stimulated by alloantigens exhibit a high degree of lysis of TNP-coupled autologous (and allogeneic) targets.

These considerations are consistent with the notion that clones of Ly123 cells bearing receptors for variants of autologous MHC products (such as those formed by virus associated with self MHC products) give rise to Ly23 memory cells which can also react to polymorphic variants of the MHC (alloantigens). This interpretation suggests two predictions: (a) early in ontogeny, alloreactive prekiller cells arise from the Ly123 and not the Ly23 pool and (b) stimulation of T cells in vitro by virus infected autologous cells should result in the generation of Ly23+ CTL that specifically lyse noninfected allogeneic target cells. The following experiments were designed to test these predictions.

**T-Cell Sets Responsible for Alloreactive Prekiller Activity During Ontogeny (Tables III, IV).** We examined the Ly phenotype of alloreactive prekiller cells in the spleens of donors at increasing intervals after birth (Table III). Spleen cells from 2-week-old B6 mice generate Ly23 cytolytic effector cells after stimulation with DBA/2 (H-2<sup>b</sup>) spleen cells (Table IV). Ly123 cells are required for generation of Ly23 alloreactive killer cells, because 1:1 mixtures of Ly1 + Ly23 cells (*i.e.*, anti-Ly1 treated cells + anti-Ly23 treated cells) did not generate significant lytic activity.

These findings indicate that the phenotype of alloreactive prekiller cells at 1 wk after birth is Ly1<sup>+</sup>2<sup>+</sup>3<sup>-</sup>. Examination of the Ly phenotype of prekiller cells of progressively older mice revealed that a substantial portion of prekiller activity resides in the Ly123 set 3 wk after birth but that by 5 wk after birth virtually all alloreactive prekiller activity was invested in cells of the Ly23 set (Table III).

**Stimulation of B6 Cells by Sendai-Modified B6 Spleen Cells Results in the Generation of CTL Specific for Both B6-Sendai Target Cells and Unmodified Allogeneic Target Cells (Table V).** B6 spleen cells were stimulated for 5 days by B6 cells coated with chemically-inactivated Sendai virus (B6-S). Such stimulation resulted in the generation of CTL that lysed B6-Sendai coated target cells but not (uncoated) syngeneic B6 target cells (Table V). In addition, the same CTL exerted substantial lytic effects on B10.BR target cells. A detailed evaluation of the specificity of the latter lysis by cold target inhibition clearly demonstrates that these alloreactive CTL also bear receptors for B6-Sendai coated cells: the lysis of B10.BR <sup>51</sup>Cr labeled targets was inhibited by the addition of B10.BR
### Table IV

**Ly Phenotype of Alloreactive Cytolytic T-Cells in Neonatal and Adult Life**

| Treatment of B6 CTL‡ | T-cells selected | Age of donor (weeks after birth) | % lysis |
|---------------------|------------------|-----------------------------------|--------|
|                     |                  | 2 wk                              | 8 wk   |
| NMS                 | All              | 55                                | 54     |
| Anti-Ly1            | Ly23             | 43                                | 48     |
| Anti-Ly23           | Ly1              | 9                                 | 2      |

* B6 spleen cells were stimulated with DBA/2 irradiated spleen cells and assayed on P815 targets at an E:T ratio of 2.2/1. Values are in percent specific release of 51Cr.

‡ NMS is CTL treated with NMS + C; anti-Ly1 is CTL treated with Ly1.2 antiserum + C; anti-Ly2 + 3 is CTL treated with Ly2.2 and Ly3.2 antiserum + C.

or B10-Sendai coated cold targets but not significantly inhibited by B10 or B10-TNP cold targets (18).

The Ly phenotype of prekiller and killer-effector cells responsible for lysis of Sendai-modified autologous cells was determined. CTL activity against both autologous Sendai-modified and unmodified allogeneic target cells was invariably mediated by Ly23 cells. Prekiller activity resided mainly in Ly123 T-cells (Table V), but was occasionally observed in Ly23 cells (data not shown).

### Discussion

These studies were undertaken to determine the cellular basis of reactivity against lymphocytes carrying MHC components that are foreign by virtue of polymorphism (alloantigens) or because of modification by chemicals or viruses (TNP-modified autologous lymphocytes). The results reported here can be summarized as follows: (a) exposure of Ly23 cells from adult mice to allogeneic cells in vitro results in the formation of Ly23+ effector cells that lyse appropriate allogeneic and chemically modified syngeneic target cells.

(b) Exposure of Ly123 cells from adult mice to chemically-modified autologous cells in vitro stimulates the development of Ly23+ effector cell progeny that lyse modified-autologous cells.

(c) Studies of the ontogeny of the T-cell sets responsible for generating alloreactive cytolytic activity indicate that early after birth (1–3 wk) alloreactive CTL are derived from Ly123 precursors cells. However, at approximately 3–5 wk of age, alloreactive prekiller activity shifts from the Ly123 compartment to the Ly23 compartment.

(d) Exposure of Ly123 T cells to autologous cells modified by chemically inactivated Sendai virus stimulates the generation of Ly23+ CTL clones that lyse both syngeneic virus-coated targets (B6-S) as well as noninfected allogeneic targets. This latter lysis reflects CTL clones that recognize B6-S antigens (18).

Based on these results we propose the following explanation for the alloreactive

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3 It should be noted, too, that this antigen stimulated Ly123→23 differentiation step is also responsible for the generation of cytotoxic effector cells against MuLV+ syngeneic lymphoma cells in B6 mice (J. C. LeClerc et al. Manuscript in preparation), and is probably responsible for the generation of CTL against syngeneic mammary tumor cells (19).
response of adult mice: continuous stimulation of Ly123 cells by autologous MHC structures associated with foreign material (e.g. virus) results in the formation of populations of Ly23 memory cells carrying receptors that bind to MHC products that are foreign due to genetic polymorphism (alloantigens). This view is supported most directly by two findings: (a) in vitro stimulation of T cells by autologous, virus-coated cells results in the formation of Ly23 + CTL that specifically lyse both syngeneic virus-infected target cells as well as uninfected allogeneic cells, and (b) early in ontogeny, prekiller activity for both TNP-coupled syngeneic and allogeneic MHC products resides in the same (Ly123 +) T-cell pool; later in ontogeny, alloreactivity is invested in Ly23 cells which, when activated, can lyse both allogeneic and TNP-coupled syngeneic target cells.

Several direct experimental predictions can be inferred from this view of alloreactivity: (a) natural exposure of mice to Sendai virus should preferentially enhance Ly23 reactivity to allogeneic cells (evidence for this is provided elsewhere (18) and tolerogenic exposure to Sendai virus might selectively diminish reactivity to allogeneic cells expressing highly cross-reactive MHC haplotypes; (b) At some time after immunization with Sendai virus in vivo, Ly23 cells should contain prekiller activity against both Sendai coated syngeneic targets and allogeneic targets after boosting in vitro with Sendai coated syngeneic cells. (c) Increased immunogenic exposure to virus-associated antigens (e.g. in the NZB mouse strain) early in ontogeny should accelerate the development and/or increase the proportion of Ly23-mediated alloreactive prekiller activity; (d) stimulation of T cells by pooled irradiated cells expressing all the MHC haplotypes of the species may be expected to generate efficient CTL against

### Table V

**Ly Phenotype of Precursors and Effector CTL Stimulated by Sendai Modified Syngeneic Antigens that Lyse Modified Syngeneic and Unmodified Allogeneic Targets**

| CTL Target | E:T  | Responder T-cell set sensitized |
|------------|------|---------------------------------|
| **Sensitization phase** | | | |
| | Unselected | Ly1 | Ly23 | Ly1 + Ly23(1:1) |
| Unselected Lyl Ly23 Lyl + Ly23(l:l) | | | | |
| B6 Anti-B6-S | 11:1 | 73 | 8 | 10 | 5 |
| B10.BR | 100:1 | 33 | 4 | 5 | ND |
| **Effector phase** | | | | |
| Unselected B6D2FI Anti-B6D2FI S | 100:1 | 70 | 16 | 60 |
| B10.RIII | 100:1 | 34 | 6 | 29 |

* 5 × 10⁸ B6 cells of the indicated T-cell set were stimulated with Sendai coated syngeneic spleen cells; Lyl cells were obtained after treatment of B6 LN cells with Ly2.2 and Ly3.2 antisera + C, and Ly23 cells were obtained after treatment of B6 LN cells with Ly1.2 antisera + C; Lyl + Ly23 cells represent 1:1 mixtures of the two cell populations. See Materials and Methods for details of treatment and culture conditions.

‡ Values represent percent specific ⁵¹Cr release against the indicated target cells (LPS-stimulated spleen cells).

§ After stimulation of B6D2FI spleen cells by Sendai coated B6D2FI spleen cells for 5 days, the remaining cells were treated with NMS or the relevant Ly serum + C (see Materials and Methods for details of procedure) to produce the indicated T-cell sets. Percent lysis produced in a 4-h assay against the indicated target cell at a 100:1 E:T ratio is shown.
(a) autologous target cells infected by a large variety of viruses, and (b) perhaps certain autologous tumor cells. Such CTL activity should be inhibited by both pooled allogeneic and virus-infected autologous cold target cells.

Recent experiments have indicated that MHC products exert important selective effects during T-cell differentiation in the thymus (20). The present studies indicate that post-thymic differentiation steps also may be driven by antigen in relationship with host MHC products: TL-Ly123+ cells may be stimulated by foreign materials associated with self MHC-products to generate Ly23 progeny that are marked by their ability to lyse allogeneic cells.

The phenomenon of alloreactivity is not limited to the generation of CTL. Disproportionately large numbers of T cells also respond to alloantigens in MLC of mouse (21), rat (8), and human (22) cells. This reaction is mainly a measure of proliferating cells, and, in the presence of a complete I-region disparity, primarily reflects the contribution of Ly1 cells (3). It will be important to determine whether a similar Ly123→Ly1 differentiation step accounts for this form of alloreactivity. If this is the case, the phenomenon of alloreactivity which heretofore appeared to lack evolutionary significance may begin to make sense in the context of immunological defense mechanisms.

Summary

We have analyzed the cellular basis of T-cell reactivity against lymphocytes expressing major histocompatibility complex (MHC) products that are foreign by virtue of polymorphism (alloantigens) or because of modification by chemicals or viruses. We find that early in ontogeny, prekiller activity against both trinitrophenyl (TNP)-coupled autologous MHC products and allogeneic MHC products resides in the same (Ly123+) T-cell pool; later in ontogeny alloreactivity is invested in Ly23 cells which, when activated, lyse TNP-coupled autologous cells as well as appropriate allogeneic target cells. We demonstrate that stimulation of Ly123+ T cells in vitro by autologous cells coated with chemically-inactivated Sendai virus results in the formation of Ly23+ cytolytic T lymphocytes (CTL) that specifically lyse both virus modified autologous target cells and unmodified allogeneic target cells.

These results suggest the following model to account for the presence of large numbers of alloreactive T-cell clones in adult animals: continuous stimulation of Ly123 cells by autologous MHC antigens associated with foreign materials such as a virus results in the formation of Ly23 memory progeny carrying receptors that recognize MHC products that are foreign due to genetic polymorphism (alloantigens). In general, these studies indicate that alloaggression (as manifest by Ly23 cells in the CTL response) reflects a high degree of cross stimulation between physiologically relevant antigens, e.g., viral determinants associated with self MHC products, and biologically irrelevant allelic variants of the MHC.

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