Reduction of Lupus Nephritis in MRL/lpr Mice by a Bacterial Superantigen Treatment

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Summary

The effects of biweekly intravenous injections of Staphylococcus Enterotoxin B (SEB) into autoimmune MRL/lpr/lpr (MRL/lpr) mice were investigated. Rather than causing the expansion of Vβ8+ T cells, SEB administration resulted in the reduction of Vβ8+, CD4−CD8− “double-negative” (DN) T cells. This was shown by FACS® analysis as this putative pathogenic population was diminished in both spleen and lymph node. The symptoms of systemic lupus erythematosus (SLE) in MRL/lpr, which include high titers of anti-DNA antibodies and circulating immune complexes and proteinuria, were reduced in SEB-treated mice in a dose-dependent manner. The clinical parameters of SLE in MRL/lpr, which include lymph node hyperplasia and necrotic vasculitis, were suppressed in 50-μg SEB-treated mice. T cells bearing Vβ6 T cell receptor, which does not interact with SEB, were not reduced with SEB administration. Thus, disease suppression was associated with a specific reduction in the number of Vβ8+, DN T cells. These results implicate a possible therapeutic role of superantigen-based immunotherapy in Vβ-restricted, T cell-dominated clinical syndromes.

Superantigens (SuperAgs)1 are molecules that in association with class II MHC activate T cells based solely on the Vβ chain of the TCR (1, 2). These antigens are the most powerful polyclonal mitogens known, stimulating a large proportion of both murine and human T cells. The minor lymphocyte stimulating (Mls) antigen, a self-SuperAg, has recently been reported to be encoded by a retrovirus, but the Mls antigen has yet to be isolated (3–7). More is known about the bacterial SuperAgs, particularly the Staphylococcus aureus enterotoxin series (SEs), whose sequence and structure have been documented (1). SuperAgs are known to exert powerful effects on the developing TCR repertoire in both CD4+ and CD8+ T cells (8–11). Previous data from this laboratory (12, 13) and others (14) have demonstrated both clonal anergy and deletion of peripheral T cells bearing reactive Vβ TCR with in vivo administration of one of these SuperAgs, Staphylococcus Enterotoxin B (SEB), which engages Vβ7 and 8–bearing T cells (2, 8).

Recent work on different animal models of disease has demonstrated a Vβ predominance of T cells involved in disease pathogenesis. Examples of this phenomenon include experimental encephalomyelitis (EAE) in B10.PL mice (15) and lupus nephritis in MRL/lpr (16), both of which show a Vβ8 restriction in T cells. Specific immunotherapies aimed at intervention at the level of these pathogenic T cells have included anti-Vβ8 antibody (Ab) (17) and Vβ8 peptide therapy (18) in EAE, and anti-T cell (Thy-1.2 [19]), CD4 [20], B220 [21]) Ab treatment in MRL/lpr mice. These treatments have resulted in both the reduction in the number of “targeted” T cells and a corresponding improvement in the disease state. These findings suggested that the TCR-binding specificity of superantigens could be exploited for downregulation of T cell, and notably, pathogenic T cell subpopulations expressing TCRs of restricted heterogeneity. We have addressed this issue by SEB immunization of autoimmune MRL/lpr mice, in which CD4−CD8− “double-negative” (DN) T cells expressing Vβ8.2 and Vβ8.3 TCRs are preferentially represented on the peripheral, pathogenic T cells (16). We demonstrate that SEB treatment in MRL/lpr mice results in a reduction in Vβ8+, CD4−CD8− peripheral T cells concomitant with disease suppression. Clinical and serological disease activity was reduced in SEB-treated mice in a dose-dependent manner.

Materials and Methods

Animals. MRL/Mp-lpr/lpr mice (4–6 wk old) were purchased from The Jackson Laboratory (Bar Harbor, ME).
Reagents and mAbs. SEB was purchased from Sigma Chemical Co. (St. Louis, MO). Reagents used for direct staining were biotin-conjugated anti-Vβ6 (22), Vβ8 (23), CD4-PE conjugate, and CD8-FITC conjugate from Becton Dickinson & Co. (Mountain View, CA). Secondary reagents, streptavidin-PE (SA-PE) and avidin-FITC, were also purchased from Becton Dickinson & Co.

Treatment of MRL/lpr with SEB. Treatment of MRL/lpr started at 6 wk of age before clinical onset of disease. Animals were injected with 50, 5, and 0.5 μg of SEB in 0.2 ml PBS or PBS alone intravenously through the tail vein every 2 wk.

Fluorescence Staining (FACS®). Spleen and axillary lymph node single cell suspensions from 6-mo-old MRL/lpr mice were treated with Tris-buffered 0.16 M ammonium chloride to lyse the RBC. 10⁶ cells were incubated with biotinylated anti-Vβ6 or anti-Vβ8 (purified from the respective B cell hybridomas by protein A-Sepharose [Pharmacia Fine Chemicals, Uppsala, Sweden]) for 30 min on ice. The cells were then washed and incubated with either SA-PE (when anti-CD8-FITC was used as the second antibody) or avidin-FITC (when anti-CD4-PE was used as the second antibody). After 30 min of incubation on ice, the cells were washed three times and incubated with anti-CD4-PE or anti-CD8-FITC (as mentioned above). Cells were washed and two-color analysis was performed by an Epics C fluorocytometer (Coulter Immunology, Hialeah, FL).

ELISA for Anti-DNA Abs and Circulating Immune Complexes. Polystyrene microtiter wells coated with double-stranded DNA (dsDNA) or goat Clq were the kind gift of Dr. Marilyn Baltz (Sigma Chemical Co.). Blood from each mouse was pooled according to treatment group and collected before the biweekly injections. Sera was diluted in 0.05% Tween 20 in PBS at a 1:500 dilution and allowed to incubate on the plates for 60 min at room temperature. The plates were then washed three times with PBS-Tween, and 50 μl of a 1:1,000 dilution of anti-IgG and anti-IgM goat anti-mouse urease conjugate (Sigma Chemical Co.) was added to the plates. After incubation for 30 min, the plates were washed three times with PBS-Tween and twice with 0.15 M NaCl. The plates were then incubated with the urease substrate solution. The urease substrate solution was made by a protocol kindly provided by Sigma Chemical Co. In short, 8 mg of bromcresol purple was dissolved in 1.48 ml of 0.01 M NaOH and then diluted to 100 ml with water. 100 mg of urea and 3.7 mg of EDTA were dissolved and the pH was adjusted to 4.8 by the addition of 0.01 M NaOH. Colourimetric change was quantified by a Microplate Reader (MR 600; Dynatech, Chantilly, VA) at 590 nm OD.

Proteinuria and Physical Symptoms. Urine (from at least four mice per group) was pooled according to treatment group. Protein concentration and the presence of blood in urine was measured semi-quantitatively by reagent strips for urine analysis (Labstix; Ames Corp., Etobicoke, Ontario). Physical symptoms were visually scored as: 0, no symptoms; 0.5, trace; 1-4, when visible symptoms are observed, with 4 being the most severe (physical symptoms include lymph node hyperplasia, immune complex vasculitis, and necrosis of the ears). Mortality was observed in the PBS and 0.5-μg SEB-treated groups at 4 mo of age. The scores representing physical

Figure 1. Circulating immune complex and anti-DNA titers as measured by ELISA. MRL/lpr/lpr mice were given biweekly intravenous injections (by tail vein) of 50, 5, and 0.5 μg of SEB in 0.2 ml PBS or PBS alone beginning at 6 wk of age. At weekly intervals, ~200 μl of blood was collected from each mouse and serum was pooled according to treatment group and stored at -20°C. (a) The results from Clq-coated plates; (b) DNA-coated wells. The data are representative of three separate experiments. Nonautoimmune C3H/HeJ and pre-autoimmune MRL/lpr (4 wk of age) registered OD readings <0.05 at 590 nm for both assays. 50 μg SEB (●), 5 μg SEB (○), 0.5 μg SEB (△), PBS (□).
symptoms were calculated by determining the total score for each group and then dividing by the number of animals alive in that group when the measurement was taken.

Results

Systemic Administration of SEB Reduces Both Immune Complex and dsDNA-specific Ab Titer. Serologically, we followed both circulating immune complex (Fig. 1 a) and ds-DNA-specific antibody (Fig. 1 b) titers as measured by ELISA. The results show that while the PBS-injected controls manifested the aggressive increase in these indices correlated with disease onset at 3 mo of age, animals treated with 50 μg SEB showed a pre-autoimmune level, similar to that measured in nonautoimmune mice. The intermediate doses of SEB (5 and 0.5 μg) decreased both serological levels 1-1.5-fold, but did not have as great an effect as the 50-μg SEB treatment, which was associated with a fourfold difference in DNA-specific OD, and an eightfold difference in immune complex OD (from this point on, “SEB treatment” will refer to the 50-μg-treated group exclusively). We have also previously observed a decrease in ds-DNA-specific Ab titer using 20 μg of SEB (unpublished observations, C. Kim). Thus, SEB treatment induces a dose-dependent decrease in two serological parameters of SLE in MKL/Ipr mice.

Specific Reduction of Vβ8+ CD4-CD8- T Cells in SEB-treated Spleens and Lymph Nodes. To ascertain the effects of SEB immunization on the peripheral Vβ8 population in this autoimmune strain, the proportions of Vβ8+ T cells in the splenic and lymph node CD4+,CD8+, and CD4-CD8- T cell populations were compared between 6-mo-old controls and 50-μg SEB-treated mice. We were curious to determine if SEB could cause a decrease in peripheral Vβ8+ T cells that were CD4+ and CD8-. The results of both splenic and lymph node analyses show that injections of SEB does produce a decrease in the Vβ8+ DN T cell fraction, from 15% to 2% in spleen (Fig. 2 a) and 22% to 2% in LN (Fig. 2 b). Interestingly, there seemed to a compensatory increase in the Vβ8+ CD4- 8- fraction with SEB treatment, from 3% to 8%. However, the Vβ8+ DN T cell proportion did not show the enormous expansion normally observed in the Vβ8+ DN T cell fraction. Also, SEB immunization led to minimal decreases in the proportions of Vβ8+ CD4+ and Vβ8+ CD8+ T cells.

The results imply that the abnormal DN T cells that are associated with both onset and acceleration of disease in the MRL/lpr strain are more susceptible to deletion than single-positive cells, and/or that SEB treatment has suppressed their time-dependent proliferation. Regardless, the results show that SEB treatment has decreased the level of these phenotypically aberrant cells and results in the suppression of disease.

Mass of Lymphoid Organs from SEB-treated MRL/lpr Mice. One of the phenotypic changes associated with disease onset is a massive lymphoid hyperplasia, which causes a profound increase in the size of lymphoid organs (24, 25). We therefore examined the splenic and lymph node sizes of mice from PBS controls and SEB-treated MRL/lpr.

As shown in Fig. 3, with SEB treatment, there is a decrease in both the spleen and the axillary lymph node. Specifically, spleens and axillary lymph nodes from PBS controls averaged 0.66 and 0.25 g, respectively. The SEB counterparts weighed 0.25 and 0.04 g. This decrease in splenic and axillary lymph node mass is due to a decrease in cell number in these lymphoid organs. The other lymph nodes demonstrated a similar decrease in cellularity and size with SEB treatment (data not shown).

Reduction in Proteinuria and the Physical Symptoms of SLE. Disease onset in these mice occurs at 3 mo of age with visible lymphoid hyperplasia, increasing titers of auto-Abs, and the development of nephritis with proteinuria. 50% mortality in the MRL/lpr strain, due to glomerulonephritis, occurs by 5 mo of age. To determine the effect of SEB treatment on
Figure 3. Mass of lymphoid organs from MLR/lpr mice. Spleen and axillary lymph nodes were removed from 6-mo-old MRL/lpr mice treated with 50 μg SEB or PBS and weighed. The data are presented as the mean mass per spleen or axillary lymph node and SD of four different experiments.

Table 1. Proteinuria

| Age (wk) | 50 μg SEB | 5 μg SEB | 0.5 μg SEB | PBS |
|----------|-----------|----------|------------|-----|
|          | g/liter   |          |            |     |
| 12       | <0.3      | <0.3     | 1.0        | 1.0 |
| 13       | <0.3      | <0.3     | 1.0        | 1.0 |
| 14       | <0.3      | <0.3     | 1.0        | 1.0 |
| 15       | <0.3      | 0.3–1.0  | 1.0*       | 1.0 |
| 16       | <0.3      | 0.3      | 1.0        | 1.0 |
| 17       | <0.3      | 1.0      | 1.0–3.0    | 1.0 |
| 18       | 0.3–1.0   | 0.3–1.0  | 3.0        | 3.0 |
| 19       | 0.3–1.0   | 0.3–1.0  | 3.0–20*    | 3.0 |
| 20       | 0.3      | 1.0–3.0  | 3.0–20*    | 3.0 |
| 21       | 0.3–1.0   | 3.0–20*  | 3.0–20*    | 3.0 |

Measured from 3 mo of age (by Labstix).
* Trace, nonhemolyzed blood.
† Hemolyzed blood.
§ Large blood.

In fact, by 21 wk of age, all the treatment groups, except 50-μg SEB, show high levels of proteinuria as well as the presence of blood in the urine, a further indicator of glomerulonephritis.

The visible physical symptoms that signal lupus in this strain include lymph node hyperplasia, necrosis of the ears, and immune complex vasculitis of the skin (24, 25). Table 2 shows that SEB treatment has been effective in suppressing the physical signs of disease and parallels the results of SEB treatment on the other parameters of SLE in the MRL/lpr strain.

Table 2. Physical Symptoms (Lymphoid Hyperplasia, Necrosis of Ear, Hair Loss)

| Age (wk) | 50 μg SEB | 5 μg SEB | 0.5 μg SEB | PBS |
|----------|-----------|----------|------------|-----|
| 12       | 0         | 0        | 0          | 0   |
| 13       | 0         | 0        | 0.3        | 0.3 |
| 14       | 0         | 0        | 0.3        | 0.3 |
| 15       | 0         | 0        | 0.35       | 0.3 |
| 16       | 0         | 0        | 0.45       | 0.4 |
| 17       | 0         | 0.1      | 0.85       | 0.6 |
| 18       | 0.1       | 0.1      | 1.1        | 0.7 |
| 19       | 0.31      | 0.31     | 0.85       | 0.6 |
| 20       | 0.31      | 0.31     | 0.85       | 1.0 |
| 21       | 0.44      | 0.95     | 0.95       | 1.06|

No symptoms, 0; trace, 0.5. Symptoms scored 1–4, (4 most severe). Total score for each group is divided by total number of mice.
expansion in lymphoid tissues is dramatically prevented in mice, the mechanisms whereby this therapy downregulates autoantibody and immune complex production are currently unclear. Previous data have demonstrated that SEB injection can cause suppression in the humoral response in normal mice (31), and thus it is possible that SEB can suppress anti-DNA antibody-producing B cells in MRL/lpr mice. The exact role of DN T cells in disease initiation and/or pathogenesis remains to be elucidated. Previous reports have shown that these cells have undergone thymic selection and expression of surface CD4 and CD8 (32, 33). There are currently two main paradigms as to the origin of these DN T cells (34). They may encode TCRs with autoreactive specificities or they may arise consequent to defective positive selection and may not have specificity for self at all. Regardless of their origins DN T cells are clearly involved in disease pathogenesis, and their abatement by SEB treatment suppresses the disease.

In an alternate approach, peptide therapy has recently been shown to be effective in both preventing and reversing EAE in Lewis rats (18). This strategy invokes a 21-amino acid peptide derived from the second complementarity determining region of the V138 TCR, and presumably induces a tolerogenic response against V138-bearing T cells. This treatment has a surprisingly rapid therapeutic effect, and the lack of foreign antigenic determinants as well as its extended regulatory effects makes this approach very promising. So far the mechanism of therapeutic effects is unclear. As yet, peptide therapy has not been investigated in the MRL/lpr strain. It would be necessary and important to compare therapeutic benefits of SEB and peptide-mediated approaches.

One potential problem associated with SEB administration in vivo is its enterotoxic effect. SEs are the common cause of food poisoning in man. However, a recent report has suggested that different portions of the SEB molecule are responsible for its T cell mitogenic and enterotoxic effects (35). Our observations support this contention, as no detrimental effect was observed in SEB-treated mice except for a transient weight loss of 5–10% in 50-μg-treated mice (data not shown; and 36).

In summary, T cell–mediated pathogenesis of autoimmunity in MRL/lpr mice is implied by the clinical improvements induced by such interventions as neonatal thymectomy (37, 38) and administration of anti-Thy-1.2 (19), CD4 (20), and B-220 (21) mAbs. This strain then provides a unique model for studying the efficacy of T cell–directed therapies at improving and/or ablating disease. We have shown that a Vβ-specific SuperAg that functionally inactivates and deletes peripheral T cells markedly reduces disease activity in these autoimmune mice. Whether Vβ-dominant T cells play a causative role in disease initiation and progression or arise through some bystander effect remains to be elucidated. However, Vβ-specific therapy by SuperAgs may have potential for future clinical application and warrants further investigation.
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