Prevention of Nephritis in Major Histocompatibility Complex Class II–deficient MRL-lpr Mice

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Summary

MRL-lpr mice develop aggressive autoimmune kidney disease associated with increased or de novo renal expression of major histocompatibility complex (MHC) class II molecules and a massive systemic expansion of CD4+CD8− double negative (DN) T cells. Whereas non-MHC linked genes can have a profound effect on the development of nephritis, lymphadenopathy, and anti-DNA antibody production in MRL-lpr mice, the role of MHC molecules has not been unequivocally established. To study the role of MHC class II in this murine model of systemic lupus erythematosus, class II–deficient MRL-lpr mice (MRL-lpr −/−) were created. MRL-lpr −/− mice developed lymphadenopathy but not autoimmune renal disease or autoantibodies. This study demonstrates that class II expression is critical for the development of autoaggressive CD4+ T cells involved in autoimmune nephritis and clearly dissociates DN T cell expansion from autoimmune disease initiation.

MRL-Mp-lpr/lpr (MRL-lpr)1 mice spontaneously develop an autoimmune disorder characterized by an immune complex glomerulonephritis, arthritis, vasculitis, and autoantibodies to nucleic acids (1). Although these mice do not precisely represent human autoimmune disease, shared immunopathologic and serologic features make this an accepted model of human SLE or lupus (2). MRL-lpr mice homozygous for the lpr gene develop massive lymphadenopathy due to the influx of abnormal double negative (DN) T cells which express CD3 but not CD4 or CD8 accessory molecules (3, 4). The lpr gene represents a loss of function mutation in the fas gene located on murine chromosome 19, resulting in defective apoptosis and DN T cell expansion (2, 5–7). Although data exists to support defects in both positive and negative thymic selection, detailed TCR Vβ repertoire analysis of CD4+, CD8+, and DN T cell populations would support the suggestion that normal thymic selection processes exist despite the absence of fas (8–10). DN cells may originate from early CD4−CD8− T cell precursors or more likely from "neglected" CD4+, CD8+, dull TCR+ T cells, with loss of accessory molecules and proliferation after escape to LN or liver mediated by a peripheral fas defect (3, 10, 11). The lpr mutation does not directly cause autoimmune disease, as the congenic strain MRL +/+ develops late onset autoimmune syndrome, and homozygous expression of the lpr gene backcrossed to nonautoimmune susceptible strains leads to lymphadenopathy and autoantibodies, but not to aggressive and rapid renal disease (12). It is therefore apparent that whereas the MRL background is required for autoimmune disease to develop, lpr accelerates rather than causes disease, and other as yet unidentified factors influence the expression of disease.

DN T cells do not appear to be essential for initiation of disease. Mice homozygous for the lpr mutation and transgenic for a class I-restricted α/β TCR specific for male (H-Y) antigen do not generate CD4−CD8− T cells yet have similar levels of autoantibodies, although the effect on lymphadenopathy may vary with mouse strains (3, 4, 13). Whereas in vitro studies of freshly isolated DN cells from MRL-lpr mice demonstrate transcription of IFN-γ and TNF-α mRNA (14), DN T cells may not produce these as biologically active cytokines in vivo (11, 15). However, these cells may not be totally functionally inert as DN T cell clones have been shown to induce MHC class II and intercellular adhesion molecule 1 (ICAM-1) expression on renal tubular cell epithelia, suggesting a role in promoting renal disease (16). Despite the massive expansion of DN T cells, increased absolute numbers of CD4+ T cells in adult MRL-lpr mice could accelerate nephritis by inducing renal MHC expression and augmenting antibody production with low-level expression of cytokines such as IFN-γ (15). Consistent with this concept, lupus

1 Abbreviations used in this paper: DN, double negative; MRL-lpr, MRL-Mp-lpr/lpr; wt, wild type.
nephritis is associated with increased or de novo renal expression of both adhesion and MHC class II molecules (17, 18). Although clinical improvement occurs with treatments leading to reduced class II expression or limiting CD4+ T cell interaction, the benefit from such treatments is limited, and a critical role for class II molecules in the development of renal immune injury has not been unequivocally established (19-22).

The advent of gene targeting in embryonic stem cells has allowed the inactivation of specific genes in the immune system to examine their function. Mice devoid of cell surface expression of MHC class II molecules have been created by introducing a loss of function mutation of the A\textsuperscript{k} gene in ES-D3 (H-2\textsuperscript{b}) cells, which have a naturally occurring mutation in their E\textsubscript{b} gene (23). Thus, the subsequent phenotype of these mice is a deficiency in the expression of both I-A and I-E molecules. To definitively test the importance of these molecules in autoimmune nephritis, we produced class II-deficient MRL-lpr mice and followed these mice for the development of kidney disease and autoantibody production. Despite the development of lymphadenopathy and DN T cell expansion, class II-deficient MRL-lpr mice did not produce IgM or IgG autoantibodies, and were protected from the aggressive autoimmune renal injury associated with this model.

Materials and Methods

**Mice.** Class II-deficient MRL-lpr mice were created by repeatedly backcrossing mice heterozygous for the disrupted A\textsuperscript{k} allele (23) to MRL-lpr/lpr mice (H-2\textsuperscript{b}) (Jackson Laboratory, Bar Harbor, ME). Mice were screened for the disrupted allele by Southern blotting of BamHI-digested tail genomic DNA, using chemiluminescent detection (Boehringer Mannheim Canada, Laval, Quebec, Canada) of a digoxigenin-labeled genomic probe for A\textsuperscript{k} as previously described (23). An F\textsubscript{6} heterozygous intercross which was more than 98% homozygous for non-MHC linked loci, produced mice homozygous for the disrupted class II A\textsuperscript{k} gene (MRL-lpr -/-) and homozygous wild-type (MRL-lpr wt/wt) control mice as well as heterozygous (MRL lpr -/wt) mice. Initial litters of 15-15 mice per group were maintained in laminar flow hoods, given sterile food and water, and treated according to Canadian Council on Animal Care guidelines.

**Materials and Histology.** Reagents were obtained from GIBCO BRL (Gaithersburg, MD), and chemicals were obtained from Sigma Chemical Co. (St. Louis, MO). The mAbs 10-2.16 (I-A\textsuperscript{k}), B21-2 (I-A\textsuperscript{d}), GKL5 (CD4), and 2.43 (CD8) (American Type Culture Collection, Rockville, MD) were prepared by protein G purification and biotinylated using a standard protocol. Supernatant from the 145-2C11 hybridoma (CD3) was kindly provided by Dr. B. Singh (University of Western Ontario, London, Canada). Histology of kidney tissue was performed using hematoxylin and eosin staining of formalin (10%-fixed kidney sections. For immunoperoxidase, kidney tissue was performed using hematoxylin and eosin staining development of kidney disease and autoantibody production.

**Flow Cytometry.** Single cell suspensions were prepared from spleens and LN of MRL-lpr wt/wt and MRL-lpr -/- mice. 1.5 x 10\textsuperscript{6} cells were dual labeled with biotinylated mAb 10-2.16 (I-A\textsuperscript{k}), GK1.5 (CD4) or 2.43 (CD8), and nonbiotinylated 145-2C11 (anti-mouse CD3). Cells were washed with HBSS, 1% FCS, and 0.1% NaN\textsubscript{3}, and then incubated with streptavidin-PE (Jackson ImmunoResearch, Avondale, PA) and a fluorescein-conjugated F(ab')\textsubscript{2}, fragment of goat anti-hamster antibody (Jackson ImmunoResearch). Cells were washed, fixed in 2% paraformaldehyde, and analyzed by flow cytometry (FACStar Plus; Becton Dickinson & Co., Mountain View, CA) using 20,000 events for each analysis.

**Clinical and Histological Scoring.** Weights and urinary protein levels were assessed weekly. Urinary protein was monitored by albumin reagent strips (Albustix; Miles) and recorded as 0-4+ (1+=0.3 g/liter, 2+=1 g/liter, 3+=3 g/liter and 4+=4 g/liter). Values >1+ are pathological in mice. Arbitrary clinical scoring of nodes was assigned by an observer blinded to group identities, using a scale of 0-4 (0 = none; 1 = a single node anywhere; 2 = bilateral axillary; femoral, or cervical nodes; 3 = generalized femoral, axillary, and cervical nodes; and 4 = massive generalized adenopathy). Serum was obtained by retro-orbital plexus sampling at 20 wk and serum creatinine levels were determined by a modified Jaffe method using an automated CX5 clinical analyzer (Beckman Instruments, Fullerton, CA). Hematoxylin and eosin-stained kidney sections were scored for histopathological glomerular damage by a blinded observer, using a scale of 0-4 as previously described (20) (0 = no involvement; 1 = mild changes in <25% of glomeruli; 2 = mild to moderate changes in 25-50%; 3 = moderate to severe changes in 50-75%, with crescent formation, and vasculitis; 4 = severe glomerulonephritis with changes in >90%, and with sclerotic glomeruli). Additionally, the degree of mononuclear cell infiltration was scored in arbitrary units 0-4 (0 = none; 1 = few in some fields; 2 = moderate in most fields; 3 = moderate in most fields; 3 = moderate in all fields; 4 = severe infiltrates with loss of normal surrounding histology).

**Results and Discussion**

**Lymphadenopathy in Class II-deficient Mice.** To prevent exposure to pathogens, all mice were isolated in laminar flow facilities and given sterile food and water. Under these conditions, mice were generally healthy and all had equivalent weight gains during the first 5-6 mo (Fig. 1). As expected,
>50% of the MRL-lpr −/− and MRL-lpr wt/wt had advanced disease by 6 mo and most were dead or required euthanasia by 7–8 mo, because of severe renal failure. Several class II-expressing homozygous MRL-lpr wt/wt and heterozygous MRL-lpr −/− mice were euthanized before 6 mo as they demonstrated advanced signs of disease. One homozygous (1/13) MRL-lpr −/− mouse was killed at 4.5 mo because of a large facial abscess, and several mice (3/12) lost weight with fur ruffling at the age of 6–7 mo, and were therefore killed. Previous reports have noted an accelerated mortality rate in nonautoimmune strains of mice homozygous for the lpr gene, possibly due to hemorrhagic necrosis of enlarged LN with secondary infection (12). None of the MRL/lpr −/− mice that were euthanized had evidence of renal failure, systemic pathogen infection, or other organ failure at the time of death.

All mice developed lymphadenopathy by 6–7 mo which was similar in magnitude in homozygous wild type, heterozygous, and class II-deficient mice (Figs. 1 and 2). The pheno-

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**Figure 1.** Analysis of weight gain and lymphadenopathy in MRL-lpr −/− mice. Littermate cohorts of equal numbers of male and female MRL-lpr wt/wt (circles), MRL-lpr −/− (diamonds), and MRL-lpr −/− (squares) (n = 13–15 mice per group) were followed. Mice were examined daily for clinical evidence of illness, and weekly for weight gain and the presence of lymphadenopathy. (A) Weight gains were equal between groups. (B and C) Most mice in all groups developed lymphadenopathy between 4 and 6 mo, and all had nodes by 7 mo (data not shown). Arbitrary clinical scoring of nodes was assigned by an observer blinded to group identities, using a scale of 0–4 in Materials and Methods. Results are represented as mean ± SEM.

**Figure 2.** Development of lymphadenopathy in MRL-lpr −/− mice. Class II-deficient MRL-lpr −/− (left, aged 4.5 mo) and class II expressing MRL-lpr wt/wt (right, aged 5 mo) mice developed massive cervical and axillary lymphadenopathy typical of mice homozygous for the lpr mutation.
Flow cytometric analysis of spleen lymphocyte subsets in class II-deficient MRL-Ipr -/- mice. Percentage of I-A<sup>k</sup> positive cells (top, upper right quadrants) decreased from >70% in MRL-Ipr wt/wt mice to <1% in MRL-Ipr -/- mice. CD3<sup>-</sup>CD8<sup>-</sup> T cells (bottom, upper right quadrants) in MRL-Ipr wt/wt mice was <10% and not detectable in MRL-Ipr -/- mice. CD3<sup>+</sup>CD8<sup>+</sup> T cells were not detected in 5-mo-old MRL-Ipr wt/wt or MRL-Ipr -/- mice (data not shown). Results are representative of three experiments, twice using one lpr wt/wt and lpr -/- mouse, and once with a single MRL-Ipr -/- mouse.

Figure 3. Flow cytometric analysis of spleen lymphocyte subsets in class II-deficient MRL-Ipr -/- mice. Percentage of I-A<sup>k</sup> positive cells (top, upper right quadrants) decreased from >70% in MRL-Ipr wt/wt mice to <1% in MRL-Ipr -/- mice. CD3<sup>+</sup>CD4<sup>+</sup> T cells (bottom, upper right quadrants) in MRL-Ipr wt/wt mice was <10% and not detectable in MRL-Ipr -/- mice. CD3<sup>+</sup>CD8<sup>+</sup> T cells were not detected in 5-mo-old MRL-Ipr wt/wt or MRL-Ipr -/- mice (data not shown). Results are representative of three experiments, twice using one lpr wt/wt and lpr -/- mouse, and once with a single MRL-Ipr -/- mouse.

Figure 4. Analysis of kidney function in MRL-Ipr -/- mice. (A and B) MRL-Ipr wt/wt (circles), MRL-Ipr -/-/wt (diamonds), and MRL-Ipr -/- (squares) mice (n = 13-15/group) were followed weekly for urinary protein. None of the MRL-Ipr -/- mice developed significant proteinuria, whereas >50% of control MRL-Ipr wt/wt and MRL-Ipr -/- mice developed proteinuria by 24 wk. (C) MRL-Ipr -/- mice had lower serum creatinine levels compared with control mice (p <0.05). Serum creatinine levels were determined in serum samples obtained from random MRL-Ipr -/- mice (n = 7) and MRL-Ipr wt/wt or MRL-Ipr -/-/wt mice (n = 7). Results are given as mean ± SEM; (*) difference from control groups (p <0.05).

Prevention of Autoimmune Nephritis in MRL-Ipr -/- Mice. Although autoimmune disease can progress independently of lymphadenopathy (4, 25), several reports have shown that neonatal thymectomy, cyclosporine, or dexamethasone, reduces lymphadenopathy and ameliorates nephritis, suggesting that a link exists between peripheral DN T cell expansion and the magnitude of autoimmune responses (4, 20, 24). Addi-
Figure 5. Comparison of kidney histology in MRL-Ipr wt/wt and MRL-Ipr −/− mice. (A) Sections from 24–28-wk-old MRL-Ipr wt/wt kidneys showed marked periglomerular infiltrates, necrotizing glomerulonephritis (open arrow) and (B) massive perivascular infiltrates with vasculitis (solid arrow), which are typical in this strain by this age. Sections from MRL-Ipr −/− mice had similar changes (data not shown). (C) In contrast, kidney structures were normal in MRL-Ipr −/− mice with normal glomeruli (open arrow) and blood vessels (solid arrow), with no marked infiltrates. Kidney MHC class II expression was assessed by immunoperoxidase using 10-2.16 (I-Ak) or B21-2 (I-Aa) mAb. Irrelevant mAb of the same isotype were used for negative controls, and control staining shown for MRL-Ipr −/− was not greater than shown for MRL-Ipr wt/wt. (D) Expression of class II was increased in tubular cells, endothelium, mesangial cells, and infiltrating cells in MRL-Ipr wt/wt mice (E), but absent in MRL-Ipr −/− (F). Staining with antibodies to I-Ak in MRL-Ipr −/− mice was not greater than background shown in (D). Figures are representative of five to seven mice in each group, with mean histopathological scores of mice presented in Table 1. x400.

Table 1. Histopathological Scoring in Renal Injury in MRL-Ipr wt/wt, MRL-Ipr −/wt and MRL-Ipr −/− Mice.

| Type              | Glomerular histology* | n  | Perivascular | Glomerular | Medulla |
|-------------------|-----------------------|----|--------------|------------|---------|
| MRL-Ipr −/−       | 1.2 ± 0.25            | 5  | 0.4 ± 0.25   | 1.0 ± 0.3  | 0.6 ± 0.25 |
| MRL-Ipr −/wt      | 3.3 ± 0.3             | 7  | 3.3 ± 0.3    | 3.0 ± 0.3  | 2.6 ± 0.5 |
| MRL-Ipr wt/wt     | 2.8 ± 0.4             | 5  | 3.8 ± 0.2    | 2.8 ± 0.2  | 1.8 ± 0.2 |

24–28-wk-old MRL mice were euthanized, and formalin-fixed kidney tissue was sectioned and stained with hematoxylin-eosin.

* Slides were scored for glomerular injury in a blinded manner, using a scale of 0–4 with 4 representing severe changes.

† Similarly, the degree of infiltration was scored in arbitrary units 0–4. A minimum of 10 fields were examined per section, counting between 20 and 30 glomeruli. Results are reported as mean ± SEM.

§ Represents difference from MRL-Ipr −/wt and MRL-Ipr wt/wt control groups (p < 0.05).
mononuclear cell infiltrates (Fig. 5, C, Table 1). It is interesting
to note that the presence of lpr-related lymphadenopathy in
nonautoimmune prone strains of mice can result in subtle
renal pathology abnormalities without overt nephritis (12).
Renal expression of class II precedes overt nephritis in MRL-
lpr mice and may be related to the local release of cytokines
(17). Kidney sections were therefore assessed to confirm loss
of class II expression in MRL-lpr --/-. In both homozygous
and heterozygous control mice, there was abundant expression
of class II on tubular epithelial cells, infiltrating
mononuclear cells, and glomerular mesangial cells (Fig. 5 E).
As expected, class II was absent in MRL-lpr --/-- kidney
sections (Fig. 5 F). Similarly, splenocytes and LN cells from
5-mo-old MRL-lpr -- mice did not express I-A^ (data not
shown).

Although MRL-lpr --/-- mice had lymphadenopathy scores
that were indistinguishable from both homozygous and hetro-
yzogous control mice (Fig. 1 C), the paucity of infiltrates
within class II-deficient kidneys might have been expected
with a previous demonstration that preferential migration
of CD4^CD8^- B220^ T cells to the kidney does not occur
and most of the infiltrating cells within the kidneys of dis-
eeased MRL-lpr mice are CD4^ T cells (26). Since CD8^- T
cells do not require CD4^ T cells for normal development
and function (27), our data suggest that autoimmune nephritis
was abrogated in these class II-deficient MRL mice by
blocking autoreactive CD4^ T cell generation within the
thymus. Alternatively, since the development of autoreactive
T cells from MRL-lpr mice in vitro has been shown to be
dependent on the presence of class II-bearing APCs (28),
it is possible that generation or proliferation of autoreactive
CD4^ T cells within the kidney may not have occurred in the
absence of renal MHC class II expression. The present
data also suggest that since lymphadenopathy occurred de-
spite blockage of normal thymic development of CD4^ T
cells, single positive CD4^ T cells are unlikely to be the
precursor T cell phenotype giving rise to DN T cells in the
periphery. This is consistent with recent data which suggest
that DN T cells are positively selected on class I but not class
II antigens (10). This hypothesis may be tested by making avail-
able CD4^ and CD8^- deficient mice backcrossed to the
MRL-lpr strain.

Autoantibody Production in Class II-deficient MRL-lpr --/--
Mice. The MRL-lpr strain of mouse also produces a large
number of autoantibodies, including those directed against
nucleic acids. The role of antibody in lupus nephritis in this
model is not entirely clear as renal disease activity may not
correlate with either antibody or immune complex levels (12,
24). Although CD4^ T cell help is required for efficient B
cell function and isotype switching, B cell hyperactivity can
proceed even if T cell proliferation is suppressed (24), and
therefore we assessed IgM and IgG anti-ssDNA antibody levels.
Both homozygous and heterozygous MRL control mice had
high levels of both antibodies while MRL-lpr --/-- mice had
essentially nondetectable levels (Fig. 6). Whereas it might
be expected that with a functional loss of CD4^ T helper
T cells in class II-deficient mice, IgG levels of all specificities
would be severely impaired in MRL-lpr --/-- mice, the loss
of IgM autoantibodies was interesting in that total IgM levels
are preserved or even elevated in nonautoimmune prone strains
of class II-deficient mice (23, 29).

In summary, MRL-lpr mice deficient of MHC class II ex-
pression do not develop autoimmune nephritis or autoanti-
bodies. It is likely that disease was prevented in this novel
strain by a lack of thymic class II expression which prevented
autoreactive T cell development. Whereas previous models
have shown dissociation of disease and autoantibody produc-
tion and various relationships between nephritis and lymph-
adenopathy, this report clearly demonstrates that with loss
of class II expression, the prevention of nephritis in an au-
toimmune susceptible strain can occur in the presence of
lymphadenopathy. Furthermore, the development of DN T
cell-derived lymphadenopathy in a class II-- and CD4 helper
cell--deficient mouse suggests these mice may become an im-
portant model in which to study the thymic and peripheral
development of these abnormal T cells.

We thank Colin C. Anderson for performing the ELISA assays, Martin White for FACS analysis, Ziquin
Yin for careful handling of the animals, and Drs. Bhagarith Singh and Abdul Abbas for review of the
manuscript and helpful comments.

This work was supported by grants from the Medical Research Council (MT-12149 to A. M. Jevnikar),
the Kidney Foundation of Canada (A. M. Jevnikar), the National Institutes of Health (AI-21569 to L. H.
Glimcher), and by gifts from the G. Harold and Leila Y. Mathers Foundation and the Richard and Jean
Ivey Foundation. A. M. Jevnikar is presently supported by the Medical Research Council of Canada and
M. J. Grusby is supported by the Arthritis Foundation and the Leukemia Society of America.
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Received for publication 14 December 1993.

References

1. Theofilopoulos, A.N., and F.J. Dixon. 1981. Etiopathogenesis of murine SLE. Immunol. Rev. 55:179.
2. Watson, M.L., J.K. Rao, G.S. Gilkeson, P. Ruiz, E.M. Eicher, D.S. Pisetsky, A. Matsuzawa, J.M. Rochelle, and M.F. Seldin. 1992. Genetic analysis of MRL-lpr mice: relationship of the Fas apoptosis gene to disease manifestations and renal disease-modifying loci. J. Exp. Med. 176:1645.
3. Zhou, T., H. Bluthmann, J. Eldridge, K. Berry, and J.D. Mountz. 1993. Origin of CD4-CD8+B220+ T cells in MRL-lpr/lpr mice. Clues from a T cell receptor beta transgenic mouse. J. Immunol. 150:3651.
4. Mountz, J.D., T. Zhou, J. Eldridge, K. Berry, and H. Bluthmann. 1990. Transgenic rearranged T cell receptor gene inhibits lymphadenopathy and accumulation of CD4+CD8+ B220+ T cells in lpr/lpr mice. J. Exp. Med. 172:1805.
5. Watanabe-Fukunaga, R., C.I. Brannan, N.G. Copeland, N.A. Jenkins, and S. Nagata. 1992. Lymphoproliferation disorder in mice explained by defects in Fas antigen that mediates apoptosis. Nature (Lond.). 356:314.
6. Wu, J., T. Zhou, J. He, and J.D. Mountz. 1993. Autoimmune disease in mice due to integration of endogenous retrovirus in an apoptosis gene. J. Exp. Med. 178:461.
7. Chu, J.-L., J. Drappa, A. Parnassa, and K.B. Elkon. 1993. The defect in Fas mRNA expression in MRL/lpr mice is associated with insertion of the retrotransposon EtAl. J. Exp. Med. 178:723.
8. Singer, P.A., R.J. McEvilly, D.J. Noonan, F.J. Dixon, and A.N. Theofilopoulos. 1986. Clonal diversity of T cell receptor beta chain variable gene expression in enlarged node of MRL-lpr/lpr lupus mice. Proc. Natl. Acad. Sci. USA. 83:7018.
9. Zou, T.H., H. Bluthmann, J. Eldridge, M. Brockhaus, K. Berry, and J.D. Mountz. 1991. Abnormal thymocyte development and production of autoreactive T cells in T cell receptor transgenic autoimmune mice. J. Immunol. 147:466.
10. Heron, L.R., R.E. Eisenberg, E. Roper, V.N. Kakkaniah, P.L. Cohen, and B.L. Kotzin. 1993. Selection of the T cell receptor repertoire in lpr/lpr mice. Cell. Immunol. 121:397.
11. Mountz, J.D., T. Zhou, J. He, and J.D. Mountz. 1993. Autoimmune disease in mice due to integration of endogenous retrovirus in an apoptosis gene. J. Exp. Med. 178:461.
12. Chu, J.-L., J. Drappa, A. Parnassa, and K.B. Elkon. 1993. The defect in Fas mRNA expression in MRL/lpr mice is associated with insertion of the retrotransposon EtA. J. Exp. Med. 178:723.
13. Singer, P.A., R.J. McEvilly, D.J. Noonan, F.J. Dixon, and A.N. Theofilopoulos. 1986. Clonal diversity of T cell receptor beta chain variable gene expression in enlarged node of MRL-lpr/lpr lupus mice. Proc. Natl. Acad. Sci. USA. 83:7018.
14. Zou, T.H., H. Bluthmann, J. Eldridge, M. Brockhaus, K. Berry, and J.D. Mountz. 1991. Abnormal thymocyte development and production of autoreactive T cells in T cell receptor transgenic autoimmune mice. J. Immunol. 147:466.
15. Heron, L.R., R.E. Eisenberg, E. Roper, V.N. Kakkaniah, P.L. Cohen, and B.L. Kotzin. 1993. Selection of the T cell receptor repertoire in lpr/lpr mice. Cell. Immunol. 121:397.
16. Tutt Landolfi, M.M., N. Van Houten, J.Q. Russell, R. Scollay, J.R. Parries, and R.C. Budd. 1993. CD2-CD4-CD8- lymph node T lymphocytes in MRL/lpr/lpr mice are derived from a CD2+CD4+CD8- thymic precursor. J. Immunol. 151:1086.
17. Izu, S., V.E. Kelley, K. Masuda, H. Yoshida, J.B. Roths, and E.D. Murphy. 1984. Induction of various autoantibodies by mutant gene lpr in several strains of mice. J. Immunol. 133:227.
18. sidman, C.L., J.D. Marshall, and H. Von Boemmer. 1992. Transgenic T cell receptor interactions in the lymphoproliferative and autoimmune syndromes of lpr and gla7 mutant mice. Eur. J. Immunol. 22:499.
19. Murray, L., and C. Martens. 1990. Abnormal T cells from lpr mice down-regulate transcription of interferon-gamma and tumor necrosis factor-alpha in vitro. Cell Immunol. 126:167.
20. Giese, T., and W.F. Davidon. 1992. Evidence for early onset, polyclonal activation of T cell subsets in mice homozygous for lpr. J. Immunol. 149:3097.
21. Diaz-Gallo, C., A.M. Jevnikar, D.C. Brennan, S. Florquin, A. Pacheco-Silva, and V. Rubin Kelley. 1992. Autoreactive kidney infiltrating T cell clones in murine lupus nephritis. Kidney Int. 42:851.
22. Wuthrich, R.P., M.A. Yui, G. Mazoujian, N. Nabavi, L.H. Glimcher, and V.E. Kelley. 1989. Enhanced MHC class II expression in renal proximal tubules precedes loss of renal function in MRL/lpr mice with lupus nephritis. Am. J. Pathol. 145:44.
23. Wuthrich, R.P., A.M. Jevnikar, T. Takei, L.H. Glimcher, and V.E. Kelley. 1990. Intercellular adhesion molecule-1 (ICAM-1) is upregulated in autoimmune lupus nephritis. Am. J. Pathol. 136:441.
24. Adelman, N.E., D.L. Watling, and H.O. McDevitt. 1983. Treatment of (NZB x NZW)F1 disease with anti-I-A monoclonal antibodies. J. Exp. Med. 158:1350.
25. Jevnikar, A.M., G.G. Singer, D.C. Brennan, H.-W. Xu, and V.E. Rubin-Kelley. 1992. Deoxymethasone prevention of autoimmune nephritis is associated with reduced renal expression of IgA but not costimulatory signals. Am. J. Pathol. 141:743.
26. Jabs, D.A., C.L. Burek, Q. Hu, R.C. Kuppers, B. Lee, and R.A. Prendergast. 1992. Anti-CD4 monoclonal antibody therapy suppresses autoimmune disease in MRL/Mp-lpr/lpr mice. Cell. Immunol. 141:496.
27. Gilkeson, G.S., R. Spurney, T.M. Coffman, R. Kurlander, P. Ruiz, and D.S. Piesky. 1992. Effect of anti-CD4 antibody treatment on inflammatory arthritis in MRL/lpr/lpr mice. Clin. Immunol. Immunopathol. 64:166.
28. Grusby, M.J., R.S. Johnson, V.E. Papaoannou, and L.H. Glimcher. 1991. Depletion of CD4+ T cells in major histocompatibility complex class II deficient mice. Science (Wash. DC). 253:1417.
29. Mountz, J.D., H.R. Smith, R.I. Wilder, J.P. Reeves, and A.D. Steinberg. 1987. CsA therapy in MRL/lpr/lpr mice: amelioration of immunotherapy despite autoantibody production. J. Exp. Med. 156:157.
30. Mountz, J.D., W.C. Gause, F.D. Finkelman, and A.D. Steinberg. 1988. Prevention of lymphadenopathy in MRL/lpr/lpr mice by blocking peripheral lymph node home with MEI-14 in vivo. J. Immunol. 140:2943.
31. Jabs, D.A., and R.A. Prendergast. 1987. Reactive lymphocytes in lacrimal gland and vasculitic renal lesions of autoimmune MRL/lpr mice express L3T3. J. Immunol. 166:1198.
32. Rahemtulla, A., W.P. Fung-Leung, M.W. Schilham, T.M. Kündig, S.R. Sambhara, A. Narendran, A. Arabian, A. Wakeham, C.J. Page, R.M. Zinkernagel, and T.W. Mak. 1991. Normal development and function of CD8+ T cells but markedly decreased helper cell activity in mice lacking CD4. Nature (Lond.). 353:180.
33. Weston, K.M., S.-T. Ju, C.Y. Lu, and M.-S. Sly. 1988. Autoreactive T cells in MRL/Mp-lpr/lpr mice: characterization of the lymphokines produced and analysis of antigen presenting cells required. J. Immunol. 141:1941.
34. Markowitz, J.S., P.R. Rogers, M.J. Grusby, D.C. Parker, and L.H. Glimcher. 1993. B lymphocyte development and activation independent of MHC class II expression. J. Immunol. 150:1223.