Lupus Nephritis in the Absence of Renal Major Histocompatibility Complex Class I and Class II Molecules

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ABSTRACT

MRL/Mp-lpr/lpr (MRL-lpr) mice develop an aggressive autoimmune disorder characterized by arthritis, vasculitis, and glomerulonephritis. Renal injury is associated with increased expression of major histocompatibility complex (MHC) molecules, as well as cytokines, adhesion molecules (intracellular adhesion molecule-1, vascular cell adhesion molecule-1), and autoantibodies. By using either MHC Class I (MRL-lpr B2m-/-) or MHC Class II deficient (MRL-lpr Ab-/-) kidneys in a transplant model, we tested the role of renal expression of these molecules in the development of autoimmune renal injury. Kidneys from MRL-lpr B2m-/- or MRL-lpr Ab-/- mice as well as control wild-type mice transplanted into MRL-lpr wt/ - recipients developed nephritis, CD4+ and CD8+ T cell infiltration, and heavy glomerular deposition of immunoglobulin. Spontaneously proliferating autoreactive T cells were found in wild-type MRL-lpr and MRL-lpr B2m-/- but not MRL-lpr Ab-/- mice. These results suggest that the absence of renal expression of either Class I or Class II molecules does not provide marked protection from autoimmune lupus nephritis and supports the possibility that protection from autoimmune disease in MRL-lpr Ab-/- mice is related to the loss of autoreactive MHC Class II-dependent CD4+ T cells.

Key Words: MHC molecules, MRL-lpr, gene deletion, β2 microglobulin, lupus nephritis

MRL/Mp-lpr/lpr (MRL-lpr) mice develop a spontaneous autoimmune disorder characterized by arthritis, vasculitis, glomerulonephritis, and autoantibodies to nucleic acids (1–4). They are an appealing model of systemic lupus erythematosus in that they have aggressive and predictable renal disease and have overlapping immunopathologic and serologic features of human systemic lupus erythematosus. Glomerular injury and tubular interstitial infiltrates are prominent by 4 months and a 50% mortality rate is evident by age 5 to 6 months (5). Overt nephritis is preceded by renal tubular expression of major histocompatibility complex (MHC) Class II molecules, and the progression of disease is associated with enhanced expression of MHC class II, as well as cytokines (interleukin [IL]-1, tumor necrosis factor-α) and adhesion molecules (intracellular adhesion molecule-1, vascular cell adhesion molecule-1) (6–12). Autoantibodies are also involved in the development of nephritis, which is often associated with the heavy deposition of immune complexes within the renal glomeruli (13–16). Therefore the development of lupus nephritis is a complex and dynamic interaction between T cells, B cells, macrophages, and renal parenchymal cells, and it includes the participation of both proinflammatory cytokines and adhesion molecules. Given the complexity of factors, it has been difficult to clarify the relative importance of renal expression of Class I and Class II molecules in the development of lupus nephritis.

The advent of gene targeting technology has allowed more definitive studies of the role of Class I and Class II molecules in vivo. The transfer of such targeted genes onto a strain background displaying unique pathobiology, such as MRL-lpr, provides an opportunity to examine the role of MHC molecules in this strain’s severe lupus syndrome. The absence of MHC Class II expression in MRL-lpr mice abrogated autoantibodies and renal injury, possibly because of the loss of autoreactive CD4+ T cells (17). However, we did not exclude a protective effect resulting from the inability of T cells to engage antigen presenting or target cells devoid of MHC within the kidney. Although introduction of a CD8+ null mutation to MRL-lpr mice does not alter autoimmune disease (18), introducing a β2 microglobulin loss-of-function mutation to MRL-lpr mice substantially reduces disease and autoantibody formation, suggesting that MHC Class I expression may play a more complex role in the selection or engagement of autoreactive T and/or B cells (19). The development of autoaggressive T cells in MRL-lpr mice is related to a defect in the deletion of peripheral autoreactive T cells by Fas-mediated apoptosis (20,21). One possibility to explain the dependence of renal disease on Class I and Class II antigens is that such autoaggressive T cells recognize and directly engage autoantigens presented by renal Class I or II, leading to renal injury. Alternatively renal injury may represent a consequence of autoaggressive T cells re-
sponding systemically or locally to antigen presented by nonrenal antigen presenting cells. In this study we used a kidney transplant model involving Class I-deficient and Class II-deficient MRL-lpr mice to discriminate between these two possibilities.

MATERIALS AND METHODS

Reagents and Monoclonal Antibodies

Reagents were obtained from Gibco BRL (Gatherersburg, MD), and chemicals were obtained from Sigma Chemical Co. (St. Louis, MO). The specific (rat antirat) monoclonal antibodies GK1.5 (anti-CD4), 53-6-72 (anti-CD8), RA3-3A1 (anti-B220), and F4/80 (antimacrophage) (American Type Culture Collection, Rockville, MD) were prepared by protein G purification of hybridoma supernatant using a standard protocol.

Kidney Transplants

All mice were housed in our colony in accordance with guidelines established by the Canadian Council on Animal Care and given water ad libitum. B2 microglobulin-deficient MRL/MpJ-lpr/lpr B2m(Dcr-mdw/mm)Dcr/lpr mice (referred to here as MRL-lpr B2m+/−/− mice) were created after 10 consecutive backcross generations of a B2m+/− stock (kindly provided by Drs. B. Koller and O. Smithies, University of North Carolina) to MRL/MpJ-lpr/lpr mice (K'B, L-A', I-E', D'α) as described (19). Class II-deficient MRL-lpr (MRL-lpr H2-Ab−/−/−) (K'B, L-A', I-E', null, D'α) mice were developed as reported previously (referred to as MRL-lpr Ab−/−) and used in this study after 10 generations of backcrossing. Donor kidneys from male and female Class II bearing wild-type MRL-lpr (MRL-lpr Ab+Ia/Ia) or heterozygous (MRL-lpr Ab+/Ia−/−) mice (K'B/k', L-A'k', I-E'null/k', D'αk/k', D'βk/k') (mean age, 13.5 ± 1.6 wk), Class II deficient MRL-lpr Ab−/−/− mice (mean age, 11.1 ± 0.8 wk), and Class I deficient MRL-lpr-lpr B2m+/−/− mice (mean age, 6.2 ± 0.9 wk) were transplanted into heterozygous H2bax male (MRL-lpr Ab+Ia/) mice (age, 12.2 ± 0.9 wk) with a technical success rate of 70% (22). Recipient mice were bilaterally nephrectomized at the time of transplantation to exclude proteinuria from a remaining contralateral kidney, and heterozygous H2bax recipient mice were used to exclude any allogeneic responses related to remaining Class I loci of the H2b embryonic stem cells used to create the original H2-Ab−/− founder mice (23). Donor mice weighed 25 to 35 g at time of transplant and had no significant proteinuria at the time of surgery. Urinary protein levels, weight, and lymphadenopathy of each mouse was assessed weekly.

Clinical and Histologic Scoring

Weights and urinary protein levels of all mice were assessed weekly. Urinary protein was monitored by albumin reagent strips (Miles, Etobicoke, ON) and recorded as 0 to 4+ (1+, 0.3 g/L; 2+, 1 g/L; 3+, 3 g/L; 4+, >4 g/L). Values >1+ were pathologic in mice. Lymph nodes were clinically scored by an observer blinded to group identities as described previously (17). Mice were euthanized when proteinuria was consistently greater than 2.5 to 3+. Serum was obtained by retro-orbital plexus of mice at the time of euthanasia, and serum creatinine levels were determined by a modified Jaffe method with an automated CX5 clinical analyzer (Beckman Instruments, Fullerton, CA). Hematoxylin and eosin-stained kidney sections were scored for histopathologic glomerular damage by a blinded observer by using a scale of 0 to 4 as described previously (0, no involvement; 1, mild changes in <25% of glomeruli; 2, mild to moderate changes in 25 to 50%; 3, moderate to severe changes in 50 to 75%, with crescent formation and vasculitis; 4, severe glomerulonephritis with changes in >90% and with sclerotic glomeruli) (17). Additionally, the degree of mononuclear cell infiltration was scored in arbitrary units of 0 to 4 (0, none; 1, few in some fields; 2, moderate in most fields; 3, moderate in all fields; 4, severe infiltrates with loss of normal surrounding histology). For immunoperoxidase labeling, cryostat sections (4 μm) of OCT (Miles, Etobicoke, ON) embedded kidney tissue were acetone fixed and incubated for 15 min with phosphate-buffered saline (PBS) containing 4% horse serum. To block nonspecific binding of biotin/avidin system components the sections were incubated with avidin D blocking solution (Blocking Kit, Vector Laboratories, Burlingame, CA) for 10 min, washed briefly with PBS, and incubated for 10 min with the biotin-blocking solution according to manufacturer's instructions. Sections were washed with PBS and incubated with optimized dilutions of primary antibody for 60 min, washed, and incubated further for 30 min with biotinylated secondary antibody; Biotin-SP-conjugated AffiniPure Goat Anti-Rat IgG (H+L) (Jackson ImmunoResearch Laboratories, West Grove, PA), diluted 1:1000 in 1% goat serum. To block endogenous peroxidase, sections were washed after incubation with secondary antibody and treated with 0.3% H2O2 in methanol for 20 min at room temperature. After washing, sections were incubated for 60 min with the avidin-biotin-peroxidase complex (Vectastain ABC kit, Vector Laboratories, Burlingame, CA). Peroxidase reactivity was detected by a 5- to 10-min incubation with 3,3'-diaminobenzidine (DAB substrate kit, Vector Laboratories, Burlingame, CA). Sections were counter stained with methyl green-alcian blue and mounted. For immunofluorescence, kidney tissue sections were first blocked for nonspecific binding in PBS containing 10% goat serum, incubated for 10 min with a 1:100 to 1:500 dilution of fluorescein isothiocyanate-conjugated goat F(ab')2 antirat immunoglobulin (Ig) G (Caltag laboratories, San Francisco, CA), washed in PBS before microscopy.

In Vitro Proliferation Assay of Autoreactive Cells

Lymph node cells from 2-month-old wild-type MRL-lpr Ab+Ia/Ia, MRL-lpr B2m+/−/−, or MRL-lpr Ab−/−/− mice were cultured at 1.3, and 5 × 10⁶ cells/well in 24-well tissue culture plates (Becton Dickinson, Paramus, NJ) by use of RPMI 1640 (Biowhittaker, Walkersville, MD) supplemented with 10% fetal calf serum, 100 U/mL penicillin-streptomycin, and 2.5 × 10⁻⁵ M 2-mercaptoethanol. After 5 days, lymph node cells were washed, recultured in 96-well microtiter plates at 2.5 × 10⁴ cells/well for 24 h, and then pulsed with 1 μCi of ³H-thymidine for an additional 24 h (24). The cultures were harvested on glass fiber filters and counted in a liquid scintillation counter (LAB Instruments, Rockville, MD).

Cytokine Detection by Reverse-Transcriptase Polymerase Chain Reaction

RNA extraction and a method for semiquantitative reverse-transcriptase polymerase chain reaction used to assay tissue for cytokine expression (IL-2, interferon-γ, IL-4, IL-10) has been described (25,26). Probes for specific cytokines were radiolabeled by primer extension with random hexanucleotides. After hybridization, blots were exposed to beta imaging screens overnight and the screens were then scanned with a phosphoimager (Bio-Rad Laboratories, Hercules, CA). Images were analyzed by densitometry using Image 1.51 (NIH, Bethesda, MD) on a Macintosh 6100 computer.
Statistics

Statistical analysis, where applicable, were performed with Statview IV software (Abacus Concepts, Berkeley, CA) on a Macintosh 6100 computer (Apple Computer, Inc., Cupertino, CA). Differences between groups were compared by one-way analysis of variance and unpaired t tests, and P < 0.05 was held to be significant. All results are expressed as mean ± SE.

RESULTS

MHC Class II or Class I Deficient Kidneys Are Not Protected from Autoimmune Injury after Transplantation

To study the ability of autoreactive T cells to mediate renal injury in the absence of renal MHC molecules, we transplanted kidneys from Class II deficient MRL-lpr Ab−/− (N = 5), Class I deficient MRL-lpr B2m−/− (N = 3), or Class II bearing (N = 4) MRL-lpr control mice into nephrectomized H2bok heterozygous (MRL-lpr Abwt/−) recipients. Such recipient mice developed nephritis equivalent to wild-type mice and were used to exclude potential allogeneic responses (17). Neither recipient nor donor mice had proteinuria before transplant, but some contralateral MRL-lpr Abwt/−, MRL-lpr Ab+/-/wt, and MRL-lpr B2m−/− donor kidneys had scattered foci of mononuclear cells in interstitial areas. In this study, transfer of passenger lymphocytes by using 12-week-old MRL-lpr Ab−/− donor kidneys transplanted into age-matched recipient mice was unlikely as renal infiltrates are absent even in much older MRL-lpr Ab−/− kidneys (17). Class I deficient MRL-lpr mice were used at 6 to 7 weeks of age to minimize any transfer of passenger lymphocytes as older MRL-lpr B2m−/− mice develop significant perivascular infiltrates and infiltration is minimal at this age in wild-type mice (19). Transplanted mice were screened weekly for proteinuria, lymphadenopathy, and weight gain. Mice had normal urine protein levels immediately posttransplant, gained weight, and developed equivalent lymphadenopathy during the study period (not shown). Mice receiving either MHC-deficient or wild-type kidneys developed mild proteinuria by 4 wk posttransplant and the level of proteinuria was not different between groups at 8 wk (Figure 1, P = 0.5). Onset of nephritis, as defined by proteinuria, was variable and was generally more rapid in Class I-deficient kidneys (7.5 ± 0.9 wk; range, 6.4–9.4 wk), although one mouse receiving a Class II-deficient kidney developed nephritis within 1 month (12.5 ± 3.1 weeks; range, 3.4–21.7 wk). There was no difference between recipients of Class II-deficient and Class II-bearing transplants (13.7 ± 3.1 wk; range, 8.8–20.5 wk). Although histomorphologic scoring of Class II-deficient kidneys suggested fewer interstitial infiltrates (range, 0 to 3+) compared with Class II bearing wild-type (range, 1 to 4+, P = 0.5), or MRL-lpr B2m−/− (range, 2 to 3+; P = 0.13) mice, differences were not different between groups (Table 1). Similarly mean serum creatinine levels at the time of euthanasia were lower in Class II-deficient kidney-transplanted mice (27 ± 4 μmol/L) than either wild-type (55 ± 19 μmol/L) or Class I-deficient transplants (46 ± 8 μmol/L), but differences did not reach statistical significance because of variance in creatinine measurements (P = 0.23).

Previous reports involving allogeneic renal transplant models have observed a reduction of infiltrating CD4+ T cells by using Class II-deficient kidneys but little influence on CD8+ T cell infiltration by using Class I-deficient kidneys (27,28). To determine whether renal expression of Class I and Class II molecules influenced the phenotype of infiltrating lymphocytes in autoimmune nephritis, we used immunoperoxidase labeling of frozen sections. There was no obvious bias toward CD4+ and CD8+ positive perivascular and interstitial T cell infiltration in Class II-deficient and control kidneys (Figure 2) or Class I-deficient kidneys (not shown). Macrophages were also detected equally in all groups and, consistent with previous reports in MRL-lpr mice, most infiltrating cells were not of the B220+ double-negative T cell phenotype (not shown) (29). With reverse-transcriptase polymerase chain reaction of RNA from Class II-deficient kidneys, we did not detect differences in the levels of IL-2, interferon-γ, IL-4, and IL-10 in MRL-lpr Ab−/− mice compared with controls, which suggested that a lack of Class II expression did not influence the proliferation of a specific TH1 or TH2 helper T cell subset (not shown). The development of lupus nephritis is associated with glomerular deposition of immunoglobulin and immune complexes. Recently, JhD-mutant mice incapable of Ig expression were crossed with the MRL-lpr strain resulting in protection from renal disease, suggesting that B cells mediate the primary injury (13). In this study, renal IgG antibody deposition was absent in Class II-deficient MRL-lpr Ab−/− mice, which do not develop IgG and IgM anti-DNA antibodies (17). In contrast, transplanted Class II-deficient kidneys developed IgG deposition similar to wild-type MRL-lpr Abwt/−/wt kidneys (Figure 3).

Class II Deletion Prevents Autoreactive T Cell Proliferation in MRL-lpr Ab−/− Mice

Lymph node (LN) cells from young MRL-lpr mice proliferate spontaneously in vitro (24). Proliferation can be blocked with anti-IA antibody and complement depletion demonstrating that proliferative responses by autoreactive CD4+ T cells are directed against "self" MHC Class II determinants. To test whether MRL-lpr Ab−/− mice can generate such self-reactive CD4+ T cells, we tested the ability of LN cells from these mice to proliferate spontaneously in vitro. LN cells from 2-month-old MRL-lpr, MRL-lpr B2m−/−, and MRL-lpr Ab−/− were cultured in vitro for 5 days. Although at this age both CD4+ and CD8+ T cells can be detected in MRL-lpr mice despite accumulating double-negative T cells, MRL-lpr Ab−/− mice lack
Figure 1. Class I and II-deficient MRL-lpr kidneys are not protected from autoimmune injury after transplantation. Bilaterally nephrectomized MRL-lpr Ab\(^{wt/}\) mice were transplanted by use of donor kidneys from MRL-lpr Ab\(^{wt/}\) or heterozygous MRL-lpr Ab\(^{wt/}\), Class I deficient MRL-lpr B2m\(^{-/-}\) and class II deficient MRL-lpr Ab\(^{-/-}\) mice. Mice were followed clinically for proteinuria (0–4+) as in "Materials and Methods." Equivalent proteinuria was noted in all groups by 8 weeks posttransplant (\(P = 0.5\)).

Peripheral CD4\(^+\) T cells because of a lack of thymic Class II expression (17). Spontaneous proliferation was detected at 5 days of culture with LN cells from MRL-lpr Ab\(^{wt/}\) and MRL-lpr B2m\(^{-/-}\) mice but not MRL-lpr Ab\(^{-/-}\) mice (Figure 4).

DISCUSSION

MRL-lpr mice are a model of aggressive multiorgan autoimmune disease. Previous work has suggested that the development of lupus nephritis represents a dynamic interaction between autoaggressive CD4\(^+\) T cells and B cells, as well as the expression of proinflammatory cytokines, MHC, and adhesion molecules within the kidney. Upregulation of several of these molecules within the kidney, in particular MHC Class II, intracellular adhesion molecule-1 and vascular cell adhesion molecule-1, precedes overt nephritis and correlates with the severity of disease (6–12). The role of renal expression of these molecules in the initiation or progression of disease remains to be established. The transfer of various inactivated or disrupted genes to autoimmune susceptible mouse strains such as MRL-lpr has improved our ability to assess the contribution of the products of these genes to the development of disease. Recently, we demonstrated that Class II-deficient MRL-lpr mice were protected from autoimmune renal disease and autoantibody formation, and suggested that this protection was caused by the loss of autoaggressive CD4\(^+\) T cells (17). This is consistent with data in which MRL-lpr CD4\(^{null}\) mice or treatment of MRL-lpr mice with anti-CD4 antibody abrogates autoimmune disease (18,30,31). Spontaneous proliferation \textit{in vitro} of lymph node cells from young MRL-lpr mice has been shown to be caused by autoreactive CD4\(^+\) T cells and can be blocked by anti-"self" Class II monoclonal antibodies (24). The demonstration in this study of spontaneously proliferating autoreactive T cells in MRL-lpr and MRL-lpr B2m\(^{-/-}\) but not MRL-lpr Ab\(^{-/-}\) mice is consistent with the possibility that protection from autoimmune disease in MRL-lpr Ab\(^{-/-}\) mice is specifically related to the loss of autoreactive CD4\(^+\) T cells. In contrast, a lack of protection...
TABLE 1. Class I and II-deficient kidneys are not protected from autoimmune injury after transplantation into heterozygous MRL-lpr recipients

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<tr>
<th>Donor Type</th>
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<th>Infiltrate</th>
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<td>Glomerular</td>
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<tr>
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<td>1.7 ± 0.3</td>
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<tr>
<td>MRL-lpr Class II bearing</td>
<td>4</td>
<td>2.0 ± 1.2</td>
<td>2.0 ± 0.6</td>
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*Hematoxylin and eosin-stained kidney sections were scored for histopathologic glomerular damage and mononuclear cell infiltration by using a scale (0 to 4+) of increasing severity as under "Materials and Methods." Improvement in glomerular injury and reduced infiltrates of MRL-lpr Ab−/− mice compared with Class II-bearing MRL-lpr (P = 0.05) or Class I-deficient MRL-lpr B2m−/− (P = 0.13) mice, was not significant.

with anti-CD8 monoclonal antibodies or introducing a CD8null mutation onto the MRL-lpr strain background suggests CD8+ T cells that have little or no effect on B cell hyperactivity, autoantibody production, or autoimmune disease (18,32). However, a β2 microglobulin deficiency in highly backcrossed MRL-lpr mice reduces both autoantibody formation and disease, providing strong support for the possibility that Class I expression plays a more complex role in the disease process (19).

In this study, we examined whether renal expression of Class I or Class II is required for injury and found that absence of these molecules was not protective, because MHC-deficient kidneys transplanted into MRL-lpr mice developed nephritis. While the modest improvement in histology and serum creatinine levels in Class II-deficient kidneys did not reach statistical significance, it is of interest that a lack of expression of Class II by renal parenchymal cells might have influenced renal injury. Direct measurements of GFR rather than determining serum creatinine levels might have demonstrated improvement in function (28). However, because all recipients of Class I and Class II-deficient kidneys developed proteinuria which was associated with abnormal renal histology, infiltrates, and heavy glomerular immunoglobulin deposition, it is unlikely that a subtle improvement in GFR or histology would reflect a significant clinical benefit in this aggressive model. It is also unlikely that transfer of passenger lymphocytes influenced the de-

Figure 2. Transplanted Class II-deficient kidneys are infiltrated with CD4+ and CD8+ T cells. Tissue sections from Class II-bearing (A-D) and Class II-deficient (E-H) donor kidneys were obtained from mice with proteinuria after transplantation. Hematoxylin and eosin stained kidney sections (A,E) from both groups demonstrated marked periglomerular infiltrates and necroting glomerulonephritis (open arrows) and massive perivascular infiltrates with vasculitis (solid arrows). For immunoperoxidase labeling (B-D, F-H), cryostat sections were incubated without specific antibody (B,F), anti-CD8+ (C,G), or anti-CD4+ (D,H) antibody as in "Materials and Methods." Perivascular (closed arrows) and interstitial infiltrates contained equivalent numbers of CD4+ and CD8+ T cells in Class I-deficient kidneys (not shown). Approximate magnification, ×300.
Figure 3. Class II-deficient kidneys are not protected from glomerular IgG deposition after transplantation. Kidney tissue sections were incubated with fluorescein isothiocyanate-conjugated goat F(ab')2 antimusle IgG and examined by immunofluorescence microscopy. Kidneys from MRL-lpr Ab−/− mice did not have IgG deposition (A) because these mice do not develop IgG autoantibodies, but glomeruli had heavy deposition after transplantation into MRL-lpr Ab wt/− recipients (C). Nontransplanted MRL-lpr Abwt/wt (B) and kidneys transplanted from Class II-bearing MRL-lpr mice which developed proteinuria after transplantation (D) had similar levels of IgG deposition.

Development of injury by using Class II-deficient donor kidneys, as MRL-lpr Ab−/− mice remain infiltrate free and renal histology is normal. Although it is possible that transfer of passenger CD4+ T cells with MRL-lpr B2m−/− kidneys, which are infiltrated in older mice, could have influenced the tempo of disease in recipient mice (19), the use of younger Class I donor kidneys did not bias the results toward protection because recipients developed nephritis rapidly after transplantation. Therefore in the MRL-lpr model, the majority of renal injury does not appear to be dependent on either renal Class I or II molecule expression. In the case of Class I, it is unlikely that renal injury is caused by renal Class I molecules rescued by circulating β2 microglobulin as we were unable to detect Class I expression by immunohistology. It is conceivable however, that expression of rescued Class I within the kidney may be below the limits of detection by immunohistology (28).

Absence of donor MHC expression in allogeneic transplant models has demonstrated that variability in protective effects depends on minor histocompatibility loci, indirect pathways of rejection, and organ-specific factors (27,28,33-35). Recently, the absence of either MHC Class I or II expression in allogeneic mouse kidney transplants was reported to reduce alloimmune injury and limit CD4+ T cell infiltration in Class II-deficient grafts (27,28). In contrast to models of renal injury caused by allogeneic transplant rejection, in this study kidneys were transplanted between congenic stocks of MRL-lpr mice to determine the specific contribution of renal MHC on injury in autoimmune lupus nephritis. The absence of a marked protective effect in our model suggests there are additional mechanisms of immune injury in lupus nephritis. The simplest explanation of our results is that autoimmune lupus nephritis is a consequence of an antibody-induced syndrome induced by the systemic activation of autoreactive T cells, and that renal Class I and II antigens may play a secondary role in kidney injury. We observed infiltration of transplanted Class I and Class II-deficient kidneys with both CD4+ and
CD8+ T cells. This suggests that a lack of renal expression of MHC per se does not influence the migration of T cells into the kidney in lupus nephritis, and it is thus possible that their attraction into the kidney is a consequence of an antibody-initiated pathologic process. The heavy deposition of IgG in glomeruli of MHC-deficient transplanted kidneys would be consistent with an important role for autoantibody in the final pathway(s) of renal injury (13–16). Alternatively in the absence of renal MHC expression, renal-derived autoantigens may be presented to T cells by indirect mechanisms within the kidney analogous to allograft rejection of MHC deficient grafts (33,34). The participation of CD4+ and CD8+ T cells in autoimmune renal injury may also occur in an antigen nonspecific manner by the localized release of cytokines and serine proteases by infiltrating CD4 and CD8+ T cells.

In summary, these results demonstrate that the absence of renal expression of either Class I or Class II molecules does not protect from autoimmune injury, and specific measures to reduce MHC expression within the kidney may not be useful clinically in preventing lupus nephritis. These results also support the suggestion that protection from autoimmune disease in MRL-lpr Ab-/- mice is related to the loss of autoreactive MHC Class II-dependent CD4+ T cells.

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Renal MHC Molecules in Lupus Nephritis


