

Major Histocompatibility Complex Class II Expression by Intrinsic Renal Cells Is Required for Crescentic Glomerulonephritis

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Summary

The requirement for major histocompatibility complex class II (MHC II) to initiate immune renal injury was studied in a murine model of CD4⁺ T cell-dependent crescentic glomerulonephritis (GN). C57BL/6 (MHC II^{+/+}) mice developed crescentic GN with glomerular CD4⁺ T cell infiltration and renal injury, in response to a nephritogenic antigen (sheep globulin) planted on their glomerular basement membrane. MHC II-deficient C57BL/6 mice (MHC II^{-/-}) did not develop crescentic GN, CD4⁺ T cell infiltration, or injury, indicating that this form of immune glomerular injury is MHC II dependent. The requirement for MHC II expression by intrinsic renal cells was studied in chimeric mice, which expressed MHC II on bone marrow-derived cells and in the thymus, but not in the kidneys. These chimeric mice had normal T and B cell populations and MHC II expression in their spleens and lymph nodes and developed an immune response to systemically and cutaneously administered sheep globulin. However, they did not develop crescentic GN, CD4⁺ T cell infiltration, or renal injury in response to the sheep globulin planted in their glomeruli. These studies demonstrate that interaction of CD4⁺ T cells with intrinsic renal cells expressing MHC II is required for development of cell-mediated immune renal injury.

Key words: major histocompatibility complex • glomerulonephritis • T lymphocyte • kidney • mice

T cell responses are normally dependent on recognition of antigen bound to MHC molecules on the surface of APCs. MHC class I molecules are predominantly associated with CD8⁺ cytotoxic T cell responses. MHC class II (MHC II) molecules present antigens to CD4⁺ T cells, which stimulate antibody production and isotype switching and act as effector cells for local cell-mediated immune responses.

“Professional” APCs are bone marrow-derived cells that present antigen to naive T cells in secondary lymphoid tissues. After activation, T cells enter nonlymphoid tissues, where they can recognize antigen and initiate local immune responses. It is well accepted that MHC II is required during activation of naive CD4⁺ T cells in secondary lymphoid tissues. However, the functional contribution of MHC II on resident cells to the effector phase of cell-mediated immune injury targeted at specific tissues *in vivo* is unknown. MHC II expression can be stimulated on cells

in many organs, including mesangial cells (1, 2) and proximal tubular cells in the kidney (3, 4). Thyroid epithelial cells expressing “aberrant” MHC II can present viral antigens to cloned human T cells *in vitro* (5).

Glomerular antibody deposition and/or accumulation of T cells is observed in the majority of cases of human glomerulonephritis (GN). These immune effectors localize in response to endogenous glomerular antigens or antigens deposited in glomeruli as components of immune complexes or because of their size or charge characteristics. In the most severe forms of human GN, glomerular injury is manifested by a “proliferative” histological pattern, accumulation of T cells and macrophages, proliferation of intrinsic glomerular cells, accumulation of cells and fibrin in Bowman’s space (“crescents”), and rapid deterioration of renal function. Studies of crescentic forms of human (6, 7) and experimental GN (8, 9) suggest an important effector role for CD4⁺ T cells. Glomerular deposition of Ig is often sparse or absent in crescentic human GN (7), and in an experimental model, crescent formation has been demonstrated to be antibody independent (10). How-

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ever, the role of glomerular MHC II expression in the local immune effector response is unknown.

MHC II-deficient mice have near complete elimination of mature CD4⁺ T cells in peripheral lymphoid organs and do not develop MHC II-dependent immune reactions (11). B cell responses to T cell-independent but not T cell-dependent antigens are preserved. These mice were used to determine the requirement for MHC II for development of crescentic GN in a CD4⁺ T cell-dependent murine model, initiated by a nephritogenic antigen planted on the glomerular basement membrane (GBM). The contribution of MHC II on intrinsic renal cells was studied in chimeric mice, which had functional CD4⁺ T cells but did not express MHC II on intrinsic renal cells.

Materials and Methods

Mice. MHC II-deficient (MHCII^{-/-}) mice, generated by targeted disruption of the MHCII Aa gene in C57BL/6 mice as described previously (11), were housed under specific pathogen-free conditions.

Generation of MHC II Chimeric Mice. Chimeric mice (B6→MHCII^{-/-}) expressing MHC II on bone marrow-derived cells but not in other organs were generated using previously described bone marrow and thymus transplantation protocols (12). MHCII^{-/-} mice were thymectomized at 4 wk of age, irradiated with 700 rad at 7 wk of age, and transplanted with T cell-depleted bone marrow from B6 (C57BL/6) mice. After an additional 4 wk, mice were engrafted under the kidney capsule with a thymus from an irradiated (900 rad) newborn wild-type (WT) mouse. B6 mice were subjected to an identical transplantation process to generate control (B6→B6) chimeras.

Assessment of Lymphocyte Populations in Chimeric Mice. Lymphocyte subsets in pooled spleen and LN cell suspensions were assessed by flow cytometry using the following mAbs: FITC-conjugated anti-B220, PE-conjugated anti-CD4, PE-conjugated anti-CD8, and FITC-conjugated anti-CD3 (PharMingen, San Diego, CA) as described previously (10). MHC II expression on B cells was assessed using FITC-conjugated anti-MHCII (PharMingen).

Induction of anti-GBM GN and Assessment of Renal Injury. Crescentic GN was initiated in mice by a single intravenous injection of 10 mg of sheep anti-GBM globulin, as described previously (13). Renal injury and other parameters were assessed 21 d later. Histological assessment was performed on 2- μ m periodic acid-Schiff-stained kidney sections. Crescent formation was assessed in a minimum of 30 glomeruli, in a blinded protocol, as described previously (13, 14). Proteinuria was determined by the Bradford method over the final 24 h of each experiment as described (15). Creatinine clearance was calculated from the serum and urine creatinine concentrations, which were measured by the alkaline picric acid method using an autoanalyzer (Cobas Bio; L. Hoffman-La Roche Ltd., Basel, Switzerland).

Assessment of Humoral and Cellular Immune Effectors in Glomeruli. Glomerular deposition of mouse IgG was assessed on cryostat-cut kidney tissue sections (4 μ m) stained with serial dilutions of FITC-conjugated sheep anti-mouse IgG (Silenus, Hawthorn, Victoria, Australia) to determine the end point titer for detection in each animal. Glomerular T cell and macrophage accumulation was assessed on cryostat-cut spleen and kidney tissue sections (6 μ m) stained to demonstrate macrophages and T cells using the

two-layer peroxidase technique as described (10). The primary antibodies were H129 (monoclonal anti-mouse CD4; American Type Culture Collection, Rockville, MD) and M1/70 (monoclonal anti-mouse Mac-1; American Type Culture Collection). Sections of spleen provided a positive control, and protein G-purified rat Ig was substituted for primary mAb to provide a negative control. A minimum of 20 equatorially sectioned glomeruli were assessed per animal, and the results were expressed as cells per glomerular cross section (c/gcs).

Assessment of the Systemic Immune Response to Sheep Globulin. Cutaneous delayed-type hypersensitivity (DTH) to the sheep globulin was assessed by intradermal challenge with 0.5 mg in 20 μ l of PBS into the hind foot of mice, 20 d after the systemic administration of sheep anti-mouse GBM globulin, as described previously (14). Ovalbumin (Sigma-Aldrich Pty. Ltd., Castle Hill, NSW, Australia) injected into the opposite foot pad was used as a control. Circulating titers of mouse anti-sheep globulin antibody were measured by ELISA as described previously (10, 14). Optical densities (405 nm) were converted to micrograms per milliliter of antibody by reference to a standard curve generated with known concentrations of bound mouse IgG. Serum from six nonimmunized mice was used as normal control. Isotypes of anti-sheep globulin antibody were also measured by ELISA at a single dilution of mouse serum optimized for each isotype (1 in 20 for IgG2a, 1 in 40 for IgG1, IgG2b, and IgG3, and 1 in 80 for IgM) using horseradish peroxidase-conjugated goat anti-mouse IgG1, IgG2a, IgG2b, IgG3, and IgM (Southern Biotechnology Associates, Inc., Birmingham, AL) at a dilution of 1:4,000.

Experimental Design and Statistical Analysis. The development of GN 21 d after anti-GBM globulin administration was studied in the following groups of mice: B6 (C57BL/6) mice ($n = 7$), MHCII^{-/-} mice ($n = 8$), B6→MHCII^{-/-} chimeric mice (MHCII^{+/+} thymus and bone marrow in MHC^{-/-} mice; $n = 8$), and B6→B6 (control) chimeric mice (MHCII^{+/+} thymus and bone marrow in MHCII^{+/+} mice; $n = 8$). In addition, measurements of baseline renal function were performed on the following separate groups of nonnephritic mice: B6 (C57BL/6) mice ($n = 8$), MHCII^{-/-} mice ($n = 7$), and B6→B6 chimeric mice ($n = 8$). Results are presented as mean \pm SEM. Statistical analysis was performed by one-way analysis of variance, with post hoc analysis using Fisher's protected least significant differences (PLSD) test.

Results

Development of Crescentic GN is MHC II Dependent. B6 (MHCII^{+/+}) mice developed severe proliferative GN (Fig. 1 A) with crescents in $56.5 \pm 5.2\%$ of glomeruli. This resulted in significant proteinuria (15.5 ± 1.5 mg/24 h; base-

Table 1. Serum Levels of Specific Mouse anti-sheep Globulin Antibody

Group	Specific serum antibody
	$\mu\text{g/ml}$
B6 with GN	125 ± 29
MHCII ^{-/-} with GN	Undetectable
B6→B6 with GN	121 ± 14
B6→MHCII ^{-/-} with GN	158 ± 34

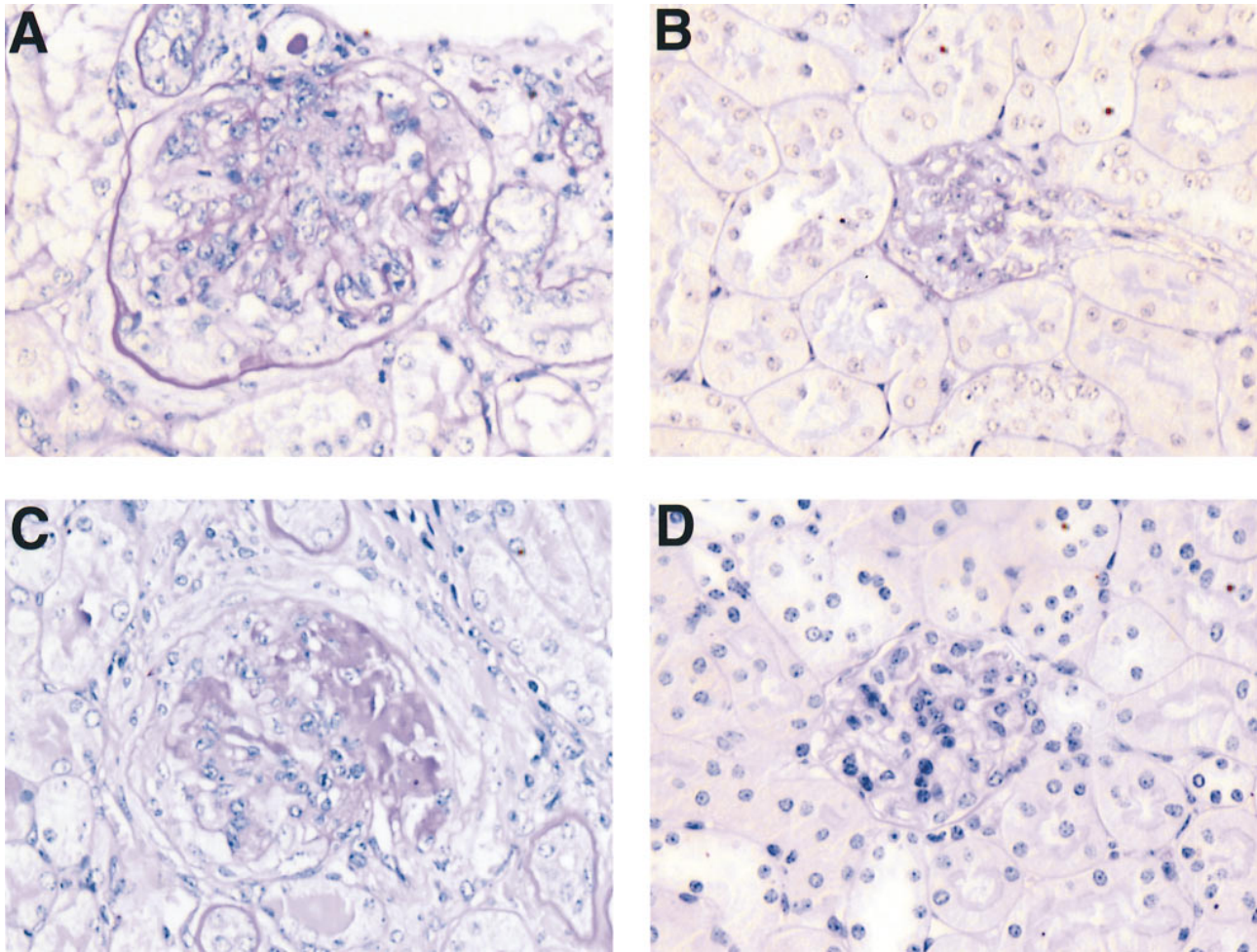


Figure 1. Histological appearance of the glomerular lesions, 21 d after anti-GBM globulin administration, in C57BL/6 (A), MHCII^{-/-} (B), B6→B6 (control) chimeric (C), and B6→MHCII^{-/-} chimeric mice (D). Periodic acid-Schiff stain, original magnification ×250.

line 2.4 ± 0.3 mg/24 h, $P < 0.0001$) and impairment of renal function (creatinine clearance, 66.4 ± 9.0 $\mu\text{l}/\text{min}$; baseline 112.4 ± 7.7 $\mu\text{l}/\text{min}$, $P = 0.0397$) (Fig. 2), and was associated with evidence of systemic and local immune responses to sheep globulin. Mouse anti-sheep globulin antibody was present in the serum (125 ± 29 $\mu\text{g}/\text{ml}$ specific mouse anti-sheep globulin antibody), and prominent linear deposition of mouse Ig was observed in glomeruli. Accumulation of CD4⁺ T cells (1.42 ± 0.37 c/gcs; normal 0.21 ± 0.4 c/gcs) and macrophages (2.21 ± 0.17 c/gcs; normal 0.37 ± 0.09 c/gcs) in glomeruli was also observed. In contrast, MHCII^{-/-} mice did not develop proliferative GN (Fig. 1 B) or crescent formation (0% of glomeruli). Proteinuria was not increased (2.7 ± 0.3 mg/24 h; baseline 2.2 ± 0.3 mg/24 h), and renal function was preserved (creatinine clearance 125.7 ± 9.1 $\mu\text{l}/\text{min}$; baseline 148.6 ± 22.9 $\mu\text{l}/\text{min}$) (Fig. 2). Specific anti-sheep globulin antibody in the serum was undetectable, as was glomerular deposition of mouse Ig. Glomerular CD4⁺ T cells (0.08 ± 0.01 c/cgs) and macrophages (0.40 ± 0.12 c/gcs) were not increased

compared with the numbers observed in normal (nonnephritic) glomeruli.

B6→MHCII^{-/-} Chimeric Mice Express MHC II in Spleen and LN Cells and Have Normal Lymphocyte Subsets. Lymphocyte subset populations and immune competence of chimeric mice were assessed 21 d after administration of anti-GBM globulin. Thymic grafts contained similar numbers of cells in both control (B6→B6) and B6→MHCII^{-/-} chimeras (B6→B6, $3.22 \pm 0.48 \times 10^7$ cells per graft; B6→MHCII^{-/-} mice, $2.06 \pm 0.14 \times 10^7$ cells per graft). Pooled splenic and LN lymphocyte populations in B6→MHCII^{-/-} mice (CD4⁺, $24.5 \pm 5.0\%$; CD8⁺, $12.1 \pm 4.5\%$; B220⁺, $45.4 \pm 8.9\%$ of CD3⁺) and B6→B6 mice (CD4⁺, $22.1 \pm 3.5\%$; CD8⁺, $10.0 \pm 1.9\%$; B220⁺, $56.2 \pm 7.0\%$ of CD3⁺) were similar to those in a normal mouse (CD4⁺, 18.6% ; CD8⁺, 11.9% ; B220⁺, 44% of CD3⁺). Their splenic and LN B cells showed similar levels of MHC II expression (Fig. 3).

B6→MHCII^{-/-} Chimeric Mice Develop a Systemic Immune Response to Sheep Globulin. The systemic immune response to sheep globulin was similar in chimeric B6→MHCII^{-/-}

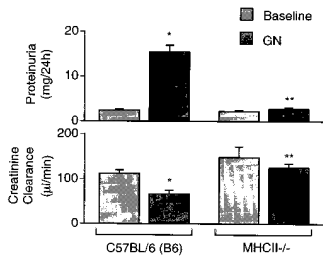


Figure 2. Proteinuria and creatinine clearance in normal (light gray bars) C57BL/6 (B6) and MHCII^{-/-} mice, and 21 d after anti-GBM globulin administration (dark gray bars). *Significantly different from baseline values. **Significantly different from WT mice with GN.

mice and B6→B6 controls. Both groups had similar amounts of specific mouse anti-sheep globulin antibody in their serum (B6→MHCII^{-/-} with GN, 158 ± 43 µg/ml; B6→B6 controls with GN, 121 ± 29 µg/ml) and similar antigen-specific Ig isotype profiles (data not shown). Antigen-specific foot pad swelling after intradermal challenge (B6→B6, 0.35 ± 0.03 mm; B6→MHCII^{-/-}, 0.27 ± 0.09 mm; WT, 0.29 ± 0.05 mm) indicated that cutaneous DTH to sheep globulin was equivalent. These data demonstrate that the CD4⁺ compartment in B6→MHCII^{-/-} mice is functional.

Absence of MHC II Expression by Intrinsic Glomerular Cells Prevents Development of Crescentic GN. Control chimeric mice (B6→B6) developed GN similar to B6 (nontransplanted) mice, with severe proliferative changes (Fig. 1 C) and crescents in 43.2 ± 8.9% of glomeruli. Deposition of mouse IgG (data not shown), accumulation of CD4⁺ T cells (1.17 ± 0.11 c/gcs) and macrophages (2.24 ± 0.14 c/gcs), and renal injury indicated by significant proteinuria (4.9 ± 1.9 mg/24 h; baseline 0.53 ± 0.10 mg/24 h, $P < 0.0001$) and reduced creatinine clearance (88.1 ± 25.5 µl/min) were similar to B6 mice with GN. In contrast, chimeric mice (B6→MHCII^{-/-}) showed no proliferative changes in glomeruli (Fig. 1 D) and did not develop crescents (0% of glomeruli). Glomerular deposition of mouse Ig was unaffected; however, accumulation of CD4⁺ T cells (0.46 ± 0.08 c/gcs) and macrophages (0.74 ± 0.21 c/gcs) was markedly reduced. These mice did not develop significant

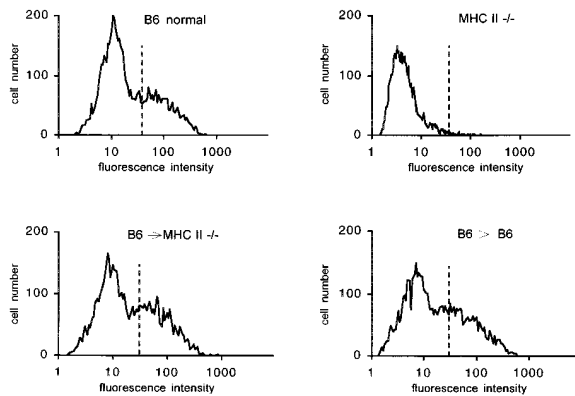


Figure 3. Flow cytometry profiles demonstrating expression of MHC II on splenic and LN cells from normal C57BL/6 and MHCII^{-/-} mice, and B6→MHCII^{-/-} and B6→B6 mice with GN. Vertical dashed lines, Upper limit for background fluorescence.

proteinuria (2.7 ± 0.3 mg/24 h, $P = 0.468$ compared with the baseline in B6→B6 mice) or impairment of renal function (creatinine clearance 122.3 ± 30.6 µl/min) (Fig. 4).

Discussion

Previous studies have demonstrated that crescentic GN in C57BL/6 mice is T cell dependent in the effector phase (14). Injury requires CD4⁺ T cell-directed macrophage accumulation (13, 14) and does not require an autologous antibody response to the planted nephritogenic antigen (10). T cells and macrophages are evident in glomeruli within 7 d of administration of anti-GBM globulin, and their numbers progressively increase to day 21, as does renal injury (13). Using this model, our current studies demonstrate the requirement for MHC II expression for the development of this cell-mediated immune renal injury. MHC II-deficient mice failed to develop a systemic immune response to the nephritogenic antigen (with no detectable circulating antigen-specific antibody or DTH when challenged cutaneously) and did not develop a local immune response when this antigen was planted in their glomeruli.

Studies of murine lupus have demonstrated that autoantibodies and renal disease do not develop in MHC II-deficient MRL/lpr mice, despite the development of lymphadenopathy and massive expansion of CD4⁺CD8⁻ (double negative) T cells (16). Renal injury in MRL/lpr mice is associated with glomerular deposition of immune complexes and is B cell dependent (17). Together with our current studies, they provide evidence for a pivotal role for MHC II in the development of both cell-mediated (CD4⁺-dependent) and antibody-dependent immune glomerular injury.

Chimeric mice were generated to identify the MHC II-expressing cell type recognized by CD4⁺ T cells in the glomerulus. They lacked MHC II expression on non-bone marrow-derived intrinsic renal cells but had normal levels of MHC II expression on bone marrow-derived cells. Analysis of spleen and LNs confirmed normal lymphocyte subsets and normal CD4⁺ to CD8⁺ T cell ratios in transplanted chimeric mice. Their systemic immune response to the nephritogenic antigen was intact. The circulating antigen-specific antibody levels and isotype profiles and the development of a local DTH reaction after cutaneous challenge demonstrated that these mice develop competent CD4⁺ T cell-dependent immune responses after antigen presentation by bone marrow-derived professional APCs.

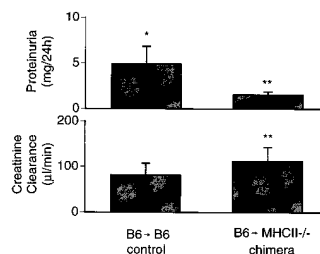


Figure 4. Proteinuria and creatinine clearance in B6→B6 (control) and B6→MHCII^{-/-} chimeric mice, 21 d after anti-GBM globulin. *Significantly different from baseline values. **Significantly different from B6 mice with GN.

However, chimeric mice lacking MHC II in their kidneys failed to develop local (CD4⁺ T cell-dependent) immune injury when the same antigen was planted in their glomeruli. This demonstrates that MHC II expression by intrinsic renal cells is required for antigen-specific CD4⁺ T cell recruitment and initiation of cell-mediated immune renal injury.

Various renal cell types, including mesangial cells (1, 2) and tubular epithelial cells (3, 4), can express MHC II. CD4⁺ T cell lines and hybridomas can recognize antigen processed and presented by proximal tubular cells (4) and thyroid epithelial cells (5) *in vitro*, although less efficiently than with antigen processed by bone marrow-derived APCs. Endothelial cells also have the capacity to express MHC II (18, 19). Our current studies were not able to define which of these cell types are recognized by CD4⁺ T cells in the kidney. Despite the existence of MHC II⁺ (Ia⁺) cells in rat glomeruli (20) and MHC II⁺ dendritic cells in rodent (21, 22) and human kidneys (23), these bone marrow-derived cells are not sufficient to target the immune response to the kidney and initiate crescentic GN.

Upregulation or novel expression of MHC II by renal cells has been demonstrated in many conditions, including allograft rejection (24), GVHD (25), lupus nephritis (26), and IgA disease (27). Tubular epithelial cells can present antigen to T cell clones derived from kidneys of MRL/lpr mice, but their ability to perform this function *in vivo* has not been clearly demonstrated (28). MHCII^{-/-} kidneys transplanted into MRL/lpr mice still develop GN and interstitial inflammatory cell infiltrates (29). This indicates that expression of MHC II by intrinsic renal cells is not required for development of this antibody-dependent form of GN, in which the immune effector response is targeted to the glomerulus (and other vascular beds) because of local immune complex deposition. In contrast, this study dem-

onstrates that GN, initiated by a planted nephritogenic antigen and directed by CD4⁺ T cells, requires MHC II expression by intrinsic renal cells. These results provide the first demonstration of the functional importance of local MHC II expression by intrinsic renal cells for targeting an immune injury to the glomerulus.

Because a systemic immune response to the nephritogenic antigen was observed, it is likely that naive CD4⁺ T cells are activated in secondary lymphoid organs by professional APCs after intravenous antigen challenge. It is unlikely that intrinsic renal cells participate in this initial priming, although we cannot exclude such a role. However, any contribution of this to the subsequent immune response would seem negligible, as chimeric mice without MHC II in their kidneys develop a systemic immune response to the nephritogenic antigen that is indistinguishable from that in normal mice. Expression of MHC II by intrinsic renal cells would appear to be functionally important in the effector phase of this disease, but was not necessary for initiation of the primary immune response.

In conclusion, these studies provide evidence for MHC II-dependent CD4⁺ T cell-directed injury in crescentic GN. In addition, they demonstrate that in the effector phase of this disease, MHC II expression by intrinsic renal cells is required to direct the CD4⁺ T cell effector response in the glomerulus, and that MHC II on bone marrow-derived cells alone is not sufficient. This provides the first demonstration of a requirement for MHC II expression by nonprofessional APCs for development of a T cell-dependent injury. The approach of transplanting MHC-intact bone marrow and thymus into MHC-deficient mice may be used to explore the role of local MHC II expression in a variety of CD4⁺ T cell-dependent organ-specific immune diseases.

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