Strain distribution pattern of immune nephritis—a follow-up study

Chun Xie1, Ziaur S. M. Rahman2, Shangkui Xie1, Jiankun Zhu1, Yong Du1, Xiangmei Qin1, Hui Zhou3, Xin J. Zhou3,*, and Chandra Mohan1,**

1Division of Rheumatology, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, USA
2Department of Microbiology and Immunology and Kimmel Cancer Center, Jefferson Medical College, Philadelphia, PA 19107, USA
3Department of Pathology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, USA

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Abstract

Previous studies have indicated that the NZW, DBA/1, 129/sv and BUB strains are particularly sensitive to experimental anti-glomerular basement membrane (GBM)-induced immune nephritis. The present study extends previous observations by examining eight additional inbred mouse strains for their susceptibility to immune nephritis. Unlike the ALR/Lt, CAST/Ei, DDY/JclSidSeyFrk, FVB/NJ, PERA/Ei, SB/Le and BALB/c strains, the C58 mouse strain was observed to be particularly susceptible to experimental immune nephritis, with CBA mice being a close second. In contrast to the other strains, C58 mice uniformly developed heavy proteinuria, azotemia and severe glomerulonephritis with prominent crescent formation and tubulointerstitial nephritis following challenge with anti-GBM sera. These differences were associated with increased murine Ig deposition, leukocyte infiltration and IFN-γ production within the kidneys of C58 mice. Studies aimed at elucidating the genetic factors and molecular pathways responsible for the enhanced renal disease in C58 mice are warranted.

Introduction

Although little is known about the genetic factors that confer renal disease susceptibility in Goodpasture's syndrome and systemic lupus erythematosus (SLE), the latter has been investigated quite extensively over the past decade, as reviewed in the studies by Vyse and Kotzin (1), Kono and Theofilopoulos (2), Wakeland and Liu (3) and Mohan (4). However, the vast majority of the nephritis susceptibility loci identified in the genetic mapping studies of lupus nephritis have also been linked to anti-nuclear auto-antibody formation. Little is known about the genetic elements that primarily dictate renal disease susceptibility in these diseases. Familial aggregation of renal disease and the frequently reported discordance between auto-antibody levels and the severity of nephritis, both in mice and human (5–10), suggest that auto-antibody formation and end-organ damage may be under distinct genetic control.

A useful tool for studying the immunology and genetics of immune nephritis is the experimental anti-glomerular basement membrane (GBM) or nephrotoxic serum (NTS) nephritis model (11, 12). In the experimentally induced nephritis model, mice are challenged with preformed rabbit anti-GBM serum, following which they rapidly develop severe glomerulonephritis (GN). In the ‘passive’ version of this model, disease is inflicted solely by the heterologous anti-GBM sera. In contrast, in the ‘active’ or ‘accelerated’ version of this model, a secondary autologous phase in which the host’s immune response to the administered (xenogenic) anti-GBM serum contributes further to the renal pathology. Hence, in the latter model, as adopted in this study, both a heterologous phase as well as an autologous phase of pathology are responsible for the ensuing renal disease. The experimental anti-GBM model has been useful in defining the respective roles of several molecules, including complement, FcR, chemokines/cytokines and their receptors, adhesion molecules, Mac-1, and the MHC molecules, in mediating auto-antibody-induced renal disease (13–30). In addition, the respective roles of host T cells and B cells in this experimental model have also...
been extensively studied (21, 23, 31–34). The contributions of various mediators and cell types toward the pathogenesis of anti-GBM disease have recently been reviewed (35).

Using this model, we had initially reported that the NZW strain, a lupus-permissive strain that harbors several major lupus susceptibility loci, exhibited more severe anti-GBM GN compared with the non-lupus-prone strains, C57BL/6 and BALB/c (11). More recently, we have identified three additional mouse genomes out of 12 inbred strains studied that also showed enhanced renal disease upon anti-GBM serum challenge (12). Genetic mapping of nephritis susceptibility loci in some of these susceptible strains is currently ongoing. In the present study, we challenged eight additional non-lupus-prone inbred strains with anti-GBM NTS, in an effort to uncover additional nephritis-permissive genomes. Out of the eight strains tested, the C58 strain emerged as an unusually nephritis-sensitive inbred strain.

Methods

Anti-GBM sera

Anti-GBM serum was generated by Lampire Biological Laboratories (Pipersville, PA, USA), as described previously (11, 12). Essentially, glomeruli from C57BL/6 mice were isolated with a series of grading sieves (150, 106 and 63 μm mesh) and sonicated for 7 min. Rabbits were next immunized with glomerular sonicates in complete Freund’s adjuvant, followed by two injections of antigen in incomplete Freund’s adjuvant (2 mg antigen per rabbit per injection), 3 weeks apart. Sera harvested from these rabbits 7 weeks after the initial injection were tested by direct immunofluorescence to demonstrate strong glomerular binding. In this report, we refer to this immune serum as ‘nephrotoxic sera’ or ‘NTS’.

Mice and anti-GBM GN

ALR/LJ (ALR), C58/J (C58), CAST/EiJ (CAST), CBA/J (CBA), DDD/HcSidSeyRkJ (DDY), FVB/NJ (FVB), PERA/EiJ (PERA), SJL/J (SJL) and BALB/cJ (BALB/c) mice were purchased from The Jackson Laboratories (Bar Harbor, ME, USA). All mice were maintained in a specific pathogen-free colony in the Animal Resource Center at University of Texas Southwestern Medical Center and studied in accordance with institutionally approved animal use guidelines. All experiments were performed in female mice at the age of 8–12 weeks. Anti-GBM nephritis was induced as described previously (12). Mice were pre-sensitized intra-peritoneal with rabbit IgG on day 0 (D0) and injected intravenous with anti-GBM serum on D14, for measuring blood urea nitrogen (BUN), using a colorimetric method developed by Sigma–Aldrich. Twenty-four-hour urine samples were collected on D0 and D14 using metabolic cages with free access to drinking water. Urinary protein concentration was determined with the Coomassie Plus Protein Assay kit from Pierce (Rockford, IL, USA). Urine creatinine was assayed using a kit purchased from Cayman Chemical (Ann Arbor, MI, USA). All animals were sacrificed on D14, kidneys were harvested, part of each was fixed in 10% neutralized formalin and part snap frozen for immunofluorescence studies.

Pathology and immunofluorescence

Three-micrometer sections cut from paraffin-embedded kidney blocks were stained with hematoxylin and eosin and periodic acid–Schiff. The slides were examined in a blinded fashion, and the severity of kidney disease was graded as reported previously (11, 12). To determine the percentage of glomeruli with crescent formation, at least 100 glomeruli were examined per kidney. For the immunofluorescence studies, 3-μm sections of frozen kidney were fixed for 10 min with cold acetone, washed with PBS and incubated with pre-titrated FITC-conjugated goat anti-rabbit IgG (Jackson ImmunoResearch Laboratories, West Grove, PA, USA). The intensity of rabbit IgG deposited in the glomeruli was graded on a scale of 0–3. In a variation of this procedure, the degree of rabbit Ig or mouse Ig deposited in the kidneys was quantitated using serial dilutions of the detection antibody, either FITC-conjugated anti-rabbit IgG or FITC-conjugated anti-mouse IgG. The numbers of intrarenal leukocytes within the glomeruli and interstitial regions were enumerated by staining with antibodies to lymphocytes (CD45 from Invitrogen, Carlsbad, CA, USA; used at 1:100 dilution) and macrophages (ER-HR3 from GenWay Biotech, San Diego, CA, USA; used at 1:50 dilution). Neutrophils were stained with the naphthol AS-D chloroacetate esterase method, using a kit purchased from Sigma.

Monitoring cytokine production

For assessing systemic T1/Th2 cytokine production, splenocytes from unmanipulated C58 and BALB/c mice were stimulated with or without plate-bound anti-CD3 and anti-CD28 (2 μg ml−1) for 5 days, after which they were treated with phorbol myristate acetate and ionomycin together with Golgi stop for 5 h. The cells were then stained for intracellular IFN-γ and IL-4 and surface CD4. Indicated are the percentages of CD4 T cells that expressed the cytokine. For assessing intrarenal cytokine production, RNA was extracted by Trizol method (Invitrogen) from the kidney cortex and medulla of C58 naive mice and BALB/c or C58 mice on D14 after induction of anti-GBM disease. RNA was reverse transcribed with TaqMan reverse transcription reagents (Applied Biosystems). Real-time reverse transcription–PCR and raw relative quantification values for INF-γ and IL-4 gene expression, using beta-actin as an endogenous control, were obtained using the ABI Prism 7000 sequence detection system (Abbott Diagnostics), TaqMan gene expression assays and universal master mix with AmpErase uracil N-glycosylase (Applied Biosystems).

ELISA

The level of xenogenic mouse anti-rabbit antibodies was determined by ELISA, as described (11, 12). Briefly, Immulon I plates (Dynatech, Chantilly, VA, USA) pre-coated with purified rabbit IgG (Sigma–Aldrich, 10 μg ml−1) were blocked, and then incubated with serially diluted mouse sera. After adding goat anti-mouse IgG conjugated to alkaline phosphatase (Jackson ImmunoResearch Laboratories), antibody binding was detected using p-nitrophenyl phosphate substrate (Sigma–Aldrich) at optical density 405. For light chains of isotype-specific ELISAs, the secondary antibody was...
substituted with rat anti-mouse kappa light chain, rabbit anti-mouse IgG1 or rabbit anti-mouse IgG2a antibody, all conjugated to biotin (Zymed Laboratories, San Francisco, CA, USA), followed by avidin–alkaline phosphatase (Roche Diagnostics, Indianapolis, IN, USA).

Statistics

Student’s t-test was performed with SigmaStat (Jandel Scientific, San Rafael, CA, USA) for comparison between any two groups.

Results

Rabbit IgG deposits in kidneys of different strains after NTS injection

Before assessing the impact of different genomes on susceptibility to immune-mediated GN, we first examined if kidneys from the different strains had been exposed to similar amounts of NTS. Fourteen days after induction of disease, the rabbit anti-GBM IgG was observed to bind exclusively to the glomerular capillary wall in a linear pattern, as depicted in Fig. 1(A). Most importantly, the kidneys from all eight inbred strains as well as from the BALB/c strain (used as a control strain that had previously been studied) exhibited equivalent amounts of rabbit IgG deposits in their glomeruli after administration of NTS (Fig. 1A and B).

Proteinuria in different inbred strains challenged with NTS

Before the induction of disease (D0), the different strains typically had urinary protein excretion of <2 mg 24 h⁻¹. Although all tested strains received the same dose of NTS and their kidneys had evidently been exposed to equivalent amounts of rabbit IgG antibodies, these strains manifested very different phenotypes, as demonstrated by their 24-h urinary protein excretion levels (Fig. 2). The ALR, PERA and SB strains did not exhibit a significant increase in proteinuria on D14, compared with D0. Though the BALB/c and CAST strains exhibited modestly elevated proteinuria on D14, these levels did not exceed 2 mg 24 h⁻¹. Compared with these strains, the CBA, DDY and FVB strains exhibited higher levels on proteinuria on D14, although significant variance was noted within each strain (Fig. 2). In contrast to all of the above strains, C58 mice uniformly developed very severe proteinuria. Out of the nine C58 mice injected with NTS, one died before D14. The eight surviving C58 mice exhibited average proteinuria of 16.6 ± 4.4 (mean ± SEM) mg 24 h⁻¹, significantly higher than that of any other strain (P < 0.05) except DDY, in which two mice developed very severe proteinuria whereas the other five exhibited mild proteinuria. These differences persisted even after normalizing against corresponding urine creatinine levels (data not shown). Thus, whereas C58 mice exhibited mean urine protein:creatinine ratios of 24.9 on D14 after anti-GBM

Fig. 1. Rabbit IgG deposits in kidneys 14 days after anti-GBM challenge. Mice of different strains were pre-sensitized with rabbit IgG and injected with NTS or pre-immune rabbit serum. The presence and localization of rabbit IgG were determined by direct immunofluorescence on D14. Photographs in (A) are representative of kidney sections from the ALR, C58 and DDY strains receiving NTS and the BALB/c strain receiving pre-immune rabbit serum (from left to right, respectively). The mean ± SEM intensity of rabbit IgG immunofluorescence in eight different strains after NTS administration is shown in (B) (n = 5–6 mice per strain), as determined using a semi-quantitative scale from 0 to 3. (The mean intensity did not differ between the different strains administered NTS.) Immunofluorescence intensity of rabbit IgG deposited in a group of BALB/c mice (n = 5) that received pre-immune rabbit serum is also shown (Ctrl, control).
challenge, the corresponding values for BALB/c was only 3.1 ($P < 0.02; N = 13$ mice each).

**BUN in NTS-challenged strains**

A similar pattern of strain difference was also noted when BUN was assayed (Fig. 3). The BALB/c, ALR and PERA strains exhibited BUN levels <30 mg dl$^{-1}$ on D0 and D14, consistent with their modest proteinuria levels (<2 mg 24 h$^{-1}$). The FVB strain exhibited significantly elevated BUN levels on D14, though the levels were modest, a pattern that is congruent to the proteinuria data for this strain. The CAST, CBA, DDY and SB strains exhibited D14 BUN levels well >30 mg dl$^{-1}$; interestingly, BUN levels were already elevated on D0 in the CAST and DDY strains, to begin with. Once again, C58 mice exhibited severe impairment of renal function. Thus, six out of eight surviving C58 mice challenged with NTS had BUN exceeding 60 mg dl$^{-1}$ (82.6 ± 17.9 mg dl$^{-1}$, mean ± SEM) on D14.

**Renal pathology in NTS-challenged strains**

We next examined the kidneys from mice on D14 after induction of anti-GBM disease. As depicted in Fig. 4, a pattern similar to that noted with proteinuria and BUN was observed among most, but not all of the inbred strains. The BALB/c, FVB and PERA strains developed minimal renal disease based on their glomerular and tubulointerstitial histology. As might be expected from the clinical data, C58 mice exhibited the most severe renal damage pathologically. GN in this strain was characterized by endocapillary and mesangial hypercellularity with increased matrix accumulation, obliteration of capillary lumens, segmental necrosis of capillary tuft and prominent crescent formation. Tubular atrophy and dilation with hyaline casts, as well as interstitial widening, were also noted (Fig. 4A). Out of seven renal specimens examined, six had GN of grade 4. Crescents were observed in the kidneys from all seven mice. Typically 15–40% (average 23.3%) of the glomeruli exhibited crescent formation.

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**Fig. 2.** Proteinuria in different strains on D14 after induction of anti-GBM disease. Mice of different strains were pre-sensitized with rabbit IgG on D0 and injected NTS on day 5. Urine samples were collected on D0 and D14 to determine total urinary protein excretion >24 h ($n = 5–8$ mice per strain). Each dot represents a single mouse. Depicted numbers at the bottom are the Student’s $t$-test $P$ values comparing proteinuria on D14 with that on D0 for each strain (upper) and comparing D14 proteinuria of each strain with that of BALB/c (lower).

**Fig. 3.** BUN in different strains on D14 after induction of anti-GBM disease. Mice of different strains were challenged with NTS. BUN levels in eight strains were monitored on D0 and D14 ($n = 5–8$ mice per strain). Each dot represents a single mouse. Depicted numbers at the bottom are the Student’s $t$-test $P$ values comparing BUN on D14 with that on D0 for each strain (upper) and comparing D14 BUN of each strain with that of BALB/c (lower).
The other strains, including ALR, CAST, CBA and DDY, demonstrated mild to moderate proliferative GN (with an average score of \(<2\)) and mild tubulointerstitial injury with very little crescent formation. Finally, the SB strain demonstrated low-grade glomerular lesions, graded at an average score of \(<2\) (Fig. 4).

**Xenogenic immune response to rabbit NTS**

Given the observation that mice of different strains developed differing degrees of renal disease despite receiving an identical glomerular-targeted immune insult, we next asked if the C58 strain that developed more severe renal disease after NTS challenge did so because of a stronger systemic xenogenic immune response to the injected rabbit IgG. As the nine strains possessed very different Igh allotypes, we focused on mouse strains that shared the same Igh allotype (type a). We therefore compared the serum levels of IgG mouse anti-rabbit antibodies in these three strains (Fig. 5A). Surprisingly, there was reduced anti-rabbit Ig in the sera of C58 mice than in BALB/c or CBA mice. Importantly, the more severe renal disease noted in C58 mice did not appear to be the consequence of a more exuberant systemic immune response. Several studies have suggested...
that a Th1-skewed immune response may determine susceptibility to anti-GBM-induced GN in response to nephritogenic antigens (20, 23, 31–34). We therefore determined the serum levels of IgG1 and IgG2a mouse anti-rabbit antibodies in the BALB/c, C58 and CBA strains after NTS challenge (Fig. 5B and C). Although IgG1 anti-rabbit antibodies in BALB/c mice were significantly higher than that in C58 and CBA mice (*P < 0.01), IgG2a anti-rabbit antibodies in the three strains did not differ from each other.

Next, we examined the kidneys of anti-GBM-assaulted C58 mice for the levels of deposited Ig. Though we had earlier noted that the different strains studied exhibited equivalent amounts of rabbit Ig deposits on their kidneys (Fig. 1), we re-executed these analyses more carefully. We performed a more quantitative analysis of the amounts of rabbit IgG and mouse IgG deposited in the kidneys of anti-GBM-assaulted C58 mice, using serial dilutions of the detection antibody. As depicted in Fig. 5(D), both the C58 kidneys and kidneys from a control strain, BALB/c, exhibited similar amounts of rabbit IgG deposits on their kidneys, thus confirming our earlier findings presented in Fig. 1. Hence, differences in the clearance rates or deposition profiles of the administered rabbit Ig are unlikely to account for the observed difference in disease outcome. Interestingly, however, at the higher dilution of the anti-mouse IgG detection antibody, the C58 kidneys exhibited higher fluorescence intensities of deposited mouse IgG, though serum levels of mouse anti-rabbit Ig were similar in both strains (Fig. 5A versus D).

Th1/Th2 skewing and leukocyte infiltrates into C58 kidneys
Next, we went on to directly evaluate systemic IFN-\(\gamma\) production (as a gauge of Th1 activity) and IL-4 production (as a gauge of Th2 activity) by C58 splenic T cells. Compared with the BALB/c control, C58-derived splenic CD4\(^+\) T cells elaborated less IFN-\(\gamma\) and IL-4, upon stimulation with anti-CD3 + anti-CD28 (Fig. 6A and B), consistent with the IgG1/ IgG2a Ig subclass distribution profiles noted above (Fig. 5). Finally, to test the possibility that the cytokine milieu within the assaulted kidneys could be different, we assayed the levels of IFN-\(\gamma\) and IL-4 with the cortex and medulla of anti-GBM-challenged C58 and control (BALB/c) kidneys. Surprisingly, the C58 kidneys revealed significantly elevated levels of IFN-\(\gamma\), suggesting that local Th1 skewing may be a contributing factor in explaining the observed strain differences in disease (Fig. 6C). In contrast, no IL-4 was detected in these samples (Fig. 6D). Moreover, the more severe renal disease in C58 kidneys was associated with significantly increased infiltration by macrophages, lymphocytes and neutrophils, compared with BALB/c kidneys, after anti-GBM challenge (Table 1).
The genetic basis of immune-mediated nephritis in Goodpasture's syndrome and SLE is poorly understood. Our previous studies had demonstrated that the NZW mouse strain was particularly susceptible to experimentally induced immune nephritis (11). More recently, we have reported that the 129/svJ, BUB/BnJ and DBA/1J strains are also susceptible to immune nephritis (12). The present work extends these studies to eight additional inbred mouse strains. The C58 strain now joins the 129/svJ, BUB/BnJ and DBA/1J strains as an additional 'normal' strain that is highly susceptible to experimentally induced immune nephritis, whereas the CBA strain emerged as a close second, both in terms of clinical disease and renal histopathology. Though individual mice in the CAST and DDY strain groups exhibited severe clinical and histological disease, the wide mouse-to-mouse variation within these two strains rendered most differences statistically insignificant.

At least two non-mutually exclusive hypotheses may explain the strain-specific difference in susceptibility to immune nephritis: systemic differences in xenogenic immune response to the injected rabbit Ig and/or renal intrinsic differences in the triggering of various local pathogenic cascades leading to GN. Our data show that the serum levels and renal deposits of rabbit Ig were not significantly higher in the disease-sensitive strains, such as C58. Hence, it appears unlikely that the difference in disease outcomes in these strains is the consequence of differences in rabbit Ig clearance or targeting to the kidneys. Interestingly and importantly, the more severe renal disease in C58 mice was associated with reduced mouse anti-rabbit antibodies in the sera (Fig. 5A) but elevated mouse anti-rabbit antibodies within the kidneys (Fig. 5D), suggesting that these specific

**Table 1.** Leukocyte infiltrates in the kidneys on D14 after anti-GBM challenge

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<tr>
<th></th>
<th>Neutrophils</th>
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<th>Lymphocytes</th>
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<th>Macrophages</th>
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<tbody>
<tr>
<td></td>
<td>BALB/C (n = 6)</td>
<td>C58 (n = 6)</td>
<td>BALB/C (n = 6)</td>
<td>C58 (n = 6)</td>
<td>BALB/C (n = 6)</td>
</tr>
<tr>
<td>Glomeruli (cells per 50 glomeruli)</td>
<td>5.4 ± 3.6</td>
<td>32.0 ± 11.4*</td>
<td>11.2 ± 5.1</td>
<td>16.0 ± 3.8</td>
<td>2.6 ± 1.9</td>
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<tr>
<td>Interstitial (cells per 20 HPF)</td>
<td>2.3 ± 1.6</td>
<td>32.5 ± 18.8*</td>
<td>22.5 ± 9.9</td>
<td>65.5 ± 18.4*</td>
<td>23.0 ± 18.8</td>
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HPF, high-power field.
*P < 0.05 (versus BALB/c; Student's t-test).

**Discussion**

The genetic basis of immune-mediated nephritis in Goodpasture's syndrome and SLE is poorly understood. Our previous studies had demonstrated that the NZW mouse strain was particularly susceptible to experimentally induced immune nephritis (11). More recently, we have reported that the 129/svJ, BUB/BnJ and DBA/1J strains are also susceptible to immune nephritis (12). The present work extends these studies to eight additional inbred mouse strains. The C58 strain now joins the 129/svJ, BUB/BnJ and DBA/1J strains as an additional 'normal' strain that is highly susceptible to experimentally induced immune nephritis, whereas the CBA strain emerged as a close second, both in terms of clinical disease and renal histopathology. Though individual mice in the CAST and DDY strain groups exhibited severe clinical and histological disease, the wide mouse-to-mouse variation within these two strains rendered most differences statistically insignificant.

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antibodies may have been selectively ‘drawn’ into the kidneys, away from the serum, by the rabbit Ig deposited upon the glomeruli of these mice. It appears that the stronger ‘systemic’ response to the administered rabbit Ig seen in C58 mice may also be associated with more exuberant leukocyte infiltrates (both lymphocytes and myeloid cells) and T<sub>N</sub>1 skewing observed within the kidneys (but not systemically). All of these leads point to potential contributions from the C58 immune system in accounting for the more severe anti-GBM disease observed. These findings are also consistent with studies from other groups that have attributed severe anti-GBM disease to T<sub>N</sub>1 skewing observed within the kidneys (but not systemically). All of these leads point to potential contributions from the C58 immune system in accounting for the more severe anti-GBM disease observed. These findings are also consistent with studies from other groups that have attributed severe anti-GBM disease to T<sub>N</sub>1 skewing observed within the kidneys (but not systemically).

In addition, it is conceivable that the intrinsic makeup of the kidneys may also be contributing (at least in part) for the enhanced immune-mediated nephritis seen in C58 mice. Thus, for example, resident renal cells (e.g. mesangial cells, epithelial cells and endothelial cells) from the disease-prone strains may be genetically programmed to aberrantly hyperrespond to the immune insult. Likewise, the nephritis-susceptible strains may somehow be better at activating infiltrating inflammatory cells in the kidneys, once immune injury is triggered. These factors may not be mutually exclusive. The relative contributions of renal intrinsic cells versus infiltrating cells in the development of immune nephritis need to be further explored.

The C58 inbred strain is known to be highly susceptible to leukemia and moderately susceptible to developing atherosclerotic aortic lesions on an atherogenic diet (36, 37). Immunocompromised C58 mice also develop immune polioencephalomyelitis following lactate dehydrogenase-elevating virus (LDV) infection (38–40). Although the C58 strain has been shown to be a high responder to dextran, and infection of C58 mice with LDV has been found to elicit auto-antibodies (41, 43), little is known about the susceptibility of this strain to autoimmune thyroiditis. It would be interesting to find whether the absence of auto-antibodies or immune complexes (57). In addition, autoantibodies to DNA, nucleosome, and other nuclear antigens is not required for the pathogenesis of lupus glomerulonephritis. J. Exp. Med. 199:255.

Among the strains that were moderately susceptible to immune nephritis, CBA is of interest because CBA mice spontaneously develop renal tubulointerstitial lesions with high frequency, without evidence of anti-tubular basement membrane auto-antibodies or immune complexes (57). In addition, this strain has been extensively used for studying experimental autoimmune thyroiditis. It would be interesting to find out if genetic elements that dictate nephritis susceptibility in this strain also confer susceptibility to the other two diseases this strain has commonly been studied for. To close, our current study has uncovered the C58 mouse strain as being exquisitely sensitive to anti-GBM-induced nephritis, with CBA mice being a close second. Studies aimed at elucidating the genetic factors and molecular pathways responsible for the enhanced renal disease in these strains are likely to be rewarding.

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Abbreviations

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<tr>
<th>Acronym</th>
<th>Description</th>
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<td>BUN</td>
<td>blood urea nitrogen</td>
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<td>D0</td>
<td>day 0</td>
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<tr>
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<td>day 14</td>
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<td>GBM</td>
<td>glomerular basement membrane</td>
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<tr>
<td>GN</td>
<td>glomerulonephritis</td>
</tr>
<tr>
<td>LDV</td>
<td>lactate dehydrogenase-elevating virus</td>
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References


