NKT Cells Inhibit the Development of Experimental Crescentic Glomerulonephritis

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ABSTRACT

CD1d is an MHC class I–like, β2-microglobulin–associated protein, constitutively expressed by antigen-presenting cells and some epithelial cells, which is recognized by NKT cells, a subpopulation of T cells. CD1d-dependent NKT cells confer protection in immune-mediated disorders, but whether these cells modulate the development of glomerulonephritis is unknown. Experimental crescentic glomerulonephritis was induced by administering anti–glomerular basement membrane antibodies to NKT cell–deficient (CD1d<sup>−/−</sup>) and wild-type mice. Compared with wild-type mice, NKT cell–deficient mice had an accelerated course of glomerulonephritis measured by renal function and crescent formation, and this was abrogated by adoptive transfer of NKT cells. Reconstitution with NKT cells also attenuated intraglomerular expression of TGF-β1 and decreased phosphorylation of the transcription factors NF-κB and IκB. Adopted transfer of fluorescence-labeled NKT cells demonstrated their distribution to glomeruli damaged by anti–glomerular basement membrane antibodies but not to the tubulointerstitium. The chemokine CXCL16, which is the ligand for CXCR6 on NKT cells, was upregulated in glomeruli after induction of glomerulonephritis, and NKT cells were present in the same glomeruli. In vitro, NKT cells inhibited LPS-stimulated proliferation of mesangial cells, an effect that was reduced by co-current treatment with an anti-CXCL16 monoclonal antibody. In summary, these findings highlight the regulatory capacity of CD1d-dependent NKT cells in experimental glomerulonephritis and suggest that CXCL16 is involved in the recruitment of these cells to the site of injury.


Despite the emerging burden of diabetic nephropathy, glomerulonephritis (GN) remains a major cause of chronic renal failure and ESRD requiring dialysis and transplantation.1,2 Although the exact nature of the pathogenesis of GN is still unknown, immune complex–mediated inflammatory responses have been suggested as central pathogenic mechanism.3 Glomerular crescent formation, the hallmark of severe and rapidly progressive immune renal injury, is characterized by the accumulation of T cells, macrophages, and fibrin in glomeruli.4–6 Among the various animal models of GN, experimental crescentic GN (ecGN) induced by anti–glomerular basement membrane (anti-GBM) antibodies has been widely studied and seems to be the most similar counterpart of the human disease.7–9

CD1d is a nonclassical MHC class I-like, β2-microglobulin–associated protein constitutively expressed by antigen-presenting cells and some epithelial cells. CD1d is recognized by a subpopulation of T cells, many of which express markers typical of NK cells and have been identified as a unique population NKT cells.10–12 A major fraction of CD1d-
restricted T cells recognize glycolipid antigen through an invariant T cell receptor (TCR) α chain. CD1d-dependent NKT cells using this invariant TCR have regulatory functions in innate and adaptive immune responses.12,13 They secrete large amounts of IL-4 and IFN-γ upon stimulation with their TCR. In animal models, NKT cells have been reported to affect the development and progression of diabetes,14 experimental autoimmune encephalitis,15 and systemic lupus erythematosus.16 NKT cells also have been exploited in several organ transplantation systems. They are critical for the induction of antigen-specific tolerance to xenogeneic islet cells induced by anti-CD4 mAb.17 NKT cells also mediate the tolerogenic action in an allogeneic heart graft model18,19 and in an allogeneic islet graft model.20

Recently, the role of regulatory cells such as CD4+CD25+ regulatory T cells was enlightened in autoimmune as well as in allogeneic disease.21,22 Although the mechanism by which CD4+CD25+ regulatory T cells regulate immune response remains controversial, cell-to-cell contact inhibition seems to be critical to exert immunosuppression.23 Wolf et al.24 reported the role of regulatory function of CD4+CD25+ T cells in an ecGN model of mice, but the role of regulatory function of NKT cells in ecGN has not been evaluated thoroughly. The objective of this study was to evaluate the regulatory capacity of CD1d-dependent NKT cells and molecular mechanisms of the reduction of glomerular injury exerted by NKT cells using an ecGN model in mice.

RESULTS

Deficiency of CD1d-Dependent NKT Cells Aggravates the ecGN

To determine the specific role of NKT cells in the development of ecGN, we induced GN in wild-type mice (B6) and B6.CD1d−/− mice that have far less NK1.1+ TCR-β+ cells in hepatic mononuclear cells compared with wild-type mice (28 versus 1.5%, B6 versus B6.CD1d−/−, respectively; Supplement Figure 1). After injection of anti-GBM Ab, B6 mice revealed the marked elevation of proteinuria and blood urea nitrogen (BUN). In B6.CD1d−/− mice, anti-GBM Ab injection induced much severe renal disease (i.e., significantly elevated proteinuria [protein/creatinine 92.7 ± 11.07 versus 177.1 ± 18.10 mg/mg, B6 versus B6.CD1d−/−, respectively; P < 0.01]) and deteriorated renal function compared with wild-type mice at 7 d of disease (BUN 73 ± 7.4 versus 123 ± 16.3 mg/dl, B6 versus B6.CD1d−/−, respectively; P < 0.05; Figure 1A), whereas the adoptive transfer of sorted NKT cells into B6.CD1d−/− mice lessened the amount of proteinuria and protected the deterioration of renal function similar to or better than wild-type mice (NKT cell transferred B6.CD1d−/−: protein/creatinine 87.2 ± 6.46 mg/mg, BUN 32 ± 2.5 mg/dl). The antiproteinuric effect of NKT cells on B6.CD1d−/− mice was dosage dependent on the numbers of cells transferred (Figure 1B). Conversely, NKT cell repletion on B6.CD1d−/− mice after the induction of ecGN (i.e., 1 d after the disease induction) did not show the significant protective effect (Supplemental Figure 2). For ex-

\[ \text{Proteinuria (mg/mg)} = 92.7 \pm 11.07 \text{ (B6)} \quad \text{versus} \quad 177.1 \pm 18.10 \text{ (B6.CD1d−/−)} \]

\[ \text{BUN (mg/dl)} = 73 \pm 7.4 \text{ (B6)} \quad \text{versus} \quad 123 \pm 16.3 \text{ (B6.CD1d−/−)} \]

\[ \text{NKT cell transferred B6.CD1d−/−: protein/creatinine 87.2 \pm 6.46 mg/mg, BUN 32 \pm 2.5 mg/dl} \]

\[ \text{NKT cell repleted on B6.CD1d−/− mice after disease induction did not show significant protective effect} \]
Histologic Changes and Presence of NKT Cells

On histologic examinations, glomerular crescents developed in more than 40% of glomeruli in B6 mice, but in B6.CD1d\(^{-/-}\) mice, the crescent formation was more prominent compared with wild-type mice (45 ± 5.0 versus 83 ± 2.5%, B6 versus B6.CD1d\(^{-/-}\), respectively; \(P < 0.05\)). Again, the repletion of NKT cells attenuated the histologic changes (i.e., less crescent formations after the adoptive transfer of NKT cells into B6.CD1d\(^{-/-}\) mice [25 ± 5.0%]; Figure 2A). To assess the molecular interactions according to presence or absence of NKT cells in host, we probed TGF-\(\beta\)1 using immunohistochemistry. The expression patterns of TGF-\(\beta\)1 were parallel with the histologic changes. TGF-\(\beta\)1 was expressed most prominently in B6.CD1d\(^{-/-}\) mice after the induction of ecGN, and its expression was downmodulated with the repletion of NKT cells into B6.CD1d\(^{-/-}\) mice similar to level in the wild-type mice (TGF-\(\beta\)1+ glomeruli; 45 ± 5.0 versus 86 ± 4.0 versus 50 ± 5.0%, B6 versus B6.CD1d\(^{-/-}\) versus B6.CD1d\(^{-/-}\) + NKT cells, respectively; \(P < 0.05\); Figure 2B). Next, we assessed the notion that NKT cells were involved in the active inflammation of ecGN. Fluorescence-tagged, sorted NKT cells were introduced into mice with the induction of anti-GBM Ab. The transferred NKT cells were detectable in 30% of glomeruli examined, and they were present in the glomeruli where Ab was deposited, but the transferred cells were not found in the tubulointerstitial area (Figure 2C). We tried to confirm again the presence of NKT cells at the site of interest again using mRNA quantification for V\(\alpha\)14 that is specific for NKT cells. As shown in Figure 2D, expression of V\(\alpha\)14 was null in B6.CD1d\(^{-/-}\) mice after PBS or anti-GBM Ab injection, but with the adoptive transfer of NKT cells into B6.CD1d\(^{-/-}\) mice with the induction of ecGN, V\(\alpha\)14 mRNA in renal tissue was upregulated in 2 h.

Figure 2. (A) NKT cell repletion lessened the crescent formation. Adoptive transfer of hepatic NKT cells (2 \(\times\) 10\(^6\)/mouse, \(-1, 0 \text{ d}\)) into B6.CD1d\(^{-/-}\) after anti-GBM Ab injection reduced cellular crescent formation and mesangial proliferation. Sections were stained with periodic acid-Schiff (PAS) reagent. Pictures were taken at 1 wk of disease. A minimum of 50 glomeruli per mouse kidney were evaluated, and the mean value was used as representative for each mouse (*\(P < 0.05\)). This represents one of three independent experiments (three mice in each group at each experiment). (B) TGF-\(\beta\)1 expression was attenuated by the repletion of NKT cells. The intraglomerular expression of TGF-\(\beta\)1 was evident after the induction of ecGN in both B6 and B6.CD1d\(^{-/-}\) mice but was markedly attenuated in NKT cell reconstituted B6.CD1d\(^{-/-}\) mice (2 \(\times\) 10\(^6\)/mouse, \(-1, 0 \text{ d}\); *\(P < 0.05\)). Pictures were taken at 1 wk of disease. Data are means ± SEM. This represents one of three independent experiments (three mice in each group at each experiment). (C) Localization of the transferred NKT cells in glomeruli. CM-Dil-labeled NKT cells (red, 2 \(\times\) 10\(^6\)/mouse, \(-1, 0 \text{ d}\)) were transferred into B6.CD1d\(^{-/-}\) mice intravenously. Kidneys were obtained at 3 h after induction of ecGN. The transferred NKT cells were easily detectable in the glomerulus, where anti-GBM Ab (green) was deposited, but the transferred cells were not found in the tubulointerstitial area. Glomerulus was evaluated using confocal laser-scanning microscopy. (D) Real-time PCR was used to determine the level of V\(\alpha\)14.Jo281 TCR mRNA that is specific for NKT cells in the glomeruli. Renal tissues were harvested at 2 and 4 h after disease induction from B6.CD1d\(^{-/-}\) mice where NKT cells were adoptively transferred. Data are means ± SEM. Magnifications: \(\times\)400 in A and B; \(\times\)800 in C.
NF-κB/IκB Interactions and NKT Cells

To probe the inflammatory check points in ecGN, we evaluated the relationships of NF-κB and IκB in this model. Anti-GBM Ab injection induced upregulation of phosphorylated p65 of NF-κB, IκBα, and TGF-β1 were measured by Western blot, and blots were reprobed with anti-β-actin antibody as a loading control. The results are representative of three separate experiments. (B) The glomerular localization of NF-κB was determined by immunofluorescence analysis. Linear deposition of anti-GBM Ab (green), p65 of NF-κB (red), and IκBα (violet) along GBM was evident in disease control mice (B6 and B6.CD1d−/−) but was markedly inhibited with the adoptive transfer of NKT cells after the induction of ecGN. DAPI was used as counterstaining. (C) NKT cells prevent complement deposition. With the induction of ecGN, C3 deposition was evident along the glomerular capillary walls and was accentuated in B6.CD1d−/− mice, but the overpopulation of NKT cells in B6 mice or the repletion of NKT cells in B6.CD1d−/− mice markedly inhibited C3 deposition along the glomerular capillary walls. (D) Macrophage/monocyte infiltration showed similar kinetics depending on the presence or absence of NKT cells. Magnification, ×800 in B.

Figure 3. (A) The repletion of NKT cells into B6.CD1d−/− mice suppressed proinflammatory proteins and TGF-β1 production. Kidneys were obtained from mice at day 7 of ecGN. The protein levels of phosphorylated p65 of NF-κB, IκBα, and TGF-β1 were measured by Western blot, and blots were reprobed with anti-β-actin antibody as a loading control. The results are representative of three separate experiments. (B) The glomerular localization of NF-κB was determined by immunofluorescence analysis. Linear deposition of anti-GBM Ab (green), p65 of NF-κB (red), and IκBα (violet) along GBM was evident in disease control mice (B6 and B6.CD1d−/−) but was markedly inhibited with the adoptive transfer of NKT cells after the induction of ecGN. DAPI was used as counterstaining. (C) NKT cells prevent complement deposition. With the induction of ecGN, C3 deposition was evident along the glomerular capillary walls and was accentuated in B6.CD1d−/− mice, but the overpopulation of NKT cells in B6 mice or the repletion of NKT cells in B6.CD1d−/− mice markedly inhibited C3 deposition along the glomerular capillary walls. (D) Macrophage/monocyte infiltration showed similar kinetics depending on the presence or absence of NKT cells. Magnification, ×800 in B.
the interactions between the phosphorylated transcriptional factors (Figure 3B). To know the protective mechanisms of NKT cells, we assessed the changes of complement deposition and cellular infiltrations depending on the presence and absence of NKT cells in ecGN. With the induction of ecGN, complement 3 (C3) deposition was evident along the glomerular capillary walls and was more prominent in B6.CD1d<sup>−/−</sup> mice, but the overpopulation of NKT cells in B6 mice and the repletion of NKT cells in B6.CD1d<sup>−/−</sup> mice markedly inhibited C3 deposition along the glomerular capillary walls where anti-GBM Ab deposited (Figure 3C). Again, macrophage/monocyte infiltration after the induction of ecGN showed the similar kinetics as complement deposition depending on the presence or absence of NKT cells in the hosts (Figure 3D).

**Cytokines are Differentially Regulated by NKT Cells in ecGN**

To test the expressions of cytokines that may affect the intraglomerular immune responses by NKT cells, we quantified mRNA levels using real-time PCR after 7 d of disease induction. With the development of ecGN in wild-type mice, TGF-β1, IFN-γ, IL-4, and IL-10 were upregulated, and these molecular changes were accentuated in B6.CD1d<sup>−/−</sup> mice except IL-4 and IL-10. The expressions of IL-4 and IL-10 were significantly suppressed in B6.CD1d<sup>−/−</sup> mice with the development of ecGN; however, these changes were reversed with the repletion of NKT cells into B6.CD1d<sup>−/−</sup> mice (Figure 4A). To test the relationship between the changes of cytokine expression and NKT cell activation, we stimulated D32.D3, an NKT cell line, with α-GalCer. As shown in Figure 4B, NKT cells produced IL-4 and IL-10 by activation.

**Expression of CXCL16 Is Parallel with NKT Cell Recruitment**

Next, we tried to evaluate the renal factor that might recruit the activated NKT cells into the affected kidney. CXCL16, which is the ligand for CXCR6, is expressed on NKT cells, and has a unique role to maintain allograft tolerance,<sup>19</sup> was probed in our model. Intraglomerular CXCL16 was not expressed in wild-type as well as in B6.CD1d<sup>−/−</sup> mice but was upregulated after the induction of ecGN in both types of mice (Figure 5A). When we traced the CM-Dil–tagged NKT cells after ecGN induction, the adoptively transferred NKT cells were found in the affected glomeruli along with the expression of CXCL16 (Figure 5B). In B6.CD1d<sup>−/−</sup> mice, the expression of CXCL16 reached the peak in 24 h after the induction of ecGN (Figure 5C), and in the adoptive transfer of NKT cells either into B6 or B6.CD1d<sup>−/−</sup> mice, the expression of CXCL16 was prominently upregulated with the induction of ecGN, thereby recruiting more NKT cells into the site of inflammation (Figure 5D).

**Direct Regulatory Capacity of NKT Cells on Mesangial Stimulation**

Finally, we further evaluated the regulatory capacity of NKT cells using an in vitro culture system. The mesangial cells were proliferated with the stimulation of LPS as assessed by MTS assay. Co-culture with D32.D3, that is NKT cell line, did not affect the proliferation of mesangial cells, but the activated NKT cells inhibited the proliferation of mesangial cells initiated by LPS stimulation; however, the inhibition of the interaction between NKT cells and mesangial cells using blocking Ab suppressed the regulatory capacity of NKT cells against exogenous stimuli (Figure 6A). The interaction between the activated NKT cells and mesangial cells was evident because the expressions of IL-4 and IL-10 were downregulated with the addition of blocking anti-CXCL16 mAb (Figure 6B).

**DISCUSSION**

In this study, we evaluated the regulatory capacity of CD1d-dependent NKT cells in ecGN. We showed that NKT cells had...
a renoprotective effect against Ab-mediated inflammation by
differential expression of various cytokines and by active en-
gagement of NKT cells at the site of inflammation. Further-
more, we demonstrated that the intraglomerular expression of
CXCL16 was associated with the recruitment of NKT cells to
the site of inflammation, thus enabling the immunoregulatory
activity.

Despite the emerging burden of diabetic nephropathy, GN
remains a major cause of chronic renal failure and ESRD re-
quiring dialysis and transplantation.1,2 Among various factors
causing GN, a central role for T cells, not only in providing help
for production of Ig but also in directing cellular immune
mechanisms, is now recognized in GN.23 Studies in murine
models have confirmed the dependence of crescentic GN in
Th1 cytokines and the ability of interventions that alter the
balance of Th1/Th2 cytokines to modulate crescentic injury.
Genetic deletion or blocking cytokines with inhibitory Ab lessened the disease severity.25 Recently, the role of cells that have regulatory function has been focused. Among them, CD4+CD25+ regulatory cells (Treg) are intensively investigated in the maintenance of tolerance in rodents and human.21 The role of Treg has been investigated in experimental GN, and demonstrated that the regulatory capacity was dependent on the number of cells reconstituted. Conversely, the protective effect of NKT cells was not evident when the cells were transferred after the induction of disease (Supplemental Figure 2). As shown in Figure 3, the presence of NKT cells prevented the deposition of C3 and monocyte infiltration, thereby lessening the immunologic downstream cascade. We assume that the readiness of NKT cells in host is critical for the control of inflammation. We further confirmed the notion that NKT cells might exert the suppressive capacity at the site of inflammation. The transferred NKT cells were traced using fluorescence labeling and real-time PCR technique. As shown in Figure 2, C and D, the transferred cells localized at the site of inflammation. We suggest that the tissue damage after Ab injection initiated NKT cell activation and the remote activation pathway applied to NKT cells (i.e., the endogenous glycolipid released after tissue damage was presented by CD1d molecules on the host antigen-presenting cells and in turn activated NKT cells in the remote place [e.g., liver]). Activated NKT cells secreted immune-modulating soluble mediators in situ and directly migrated to and acted at the site of inflammation.28,29 Previous studies by us and other researchers on the immunoregulatory functions of NKT cells have emphasized the key role of various cytokines. IL-4, IL-10, and TGF-β1 seemed to mediate the immunoregulatory activity of NKT cells in different experimental models.26,30,31 Although TGF-β1 is a multifunctional cytokine that has diverse effects on a variety of cell types, blockade of its signaling prevented the development of ecGN,32 and the expression of TGF-β1 was positively correlated with the severity of ecGN as in this study. With the development of ecGN, inflammatory pathways were activated and it was reflected in the upregulation of phosphorylated p65 in our experiment. The absence of NKT cells that exert immunosuppressive activity accentuated the activation of transcriptional factors. The expressions of various cytokines were parallel with the changes of transcriptional factors. In our model, IL-4 and IL-10 expressions were repressed in NKT cell–deficient mice, and the repletion of NKT cells made the cytokine profiles similar to wild-type hosts. These findings are consistent with the previous report that NKT cells secreted IL-4 and IL-10 robustly with the activation.10,28 Recently, it was reported that CXCL16/CXCR6 pathway was critical for the NKT cell trafficking and CXCL16 upregulation was associated the induction of allograft tolerance.19 CXCL16 was discovered as a ligand for CXCR6 that is expressed on activated T and NKT cells and is a membrane-bound chemokine.33,34 We hypothesized that renal injury mediated by anti-GBM Ab might induce the intraglomerular upregulation of CXCL16. As shown in Figure 5A, CXCL16 was
expressed evidently by the induction of ecGN regardless of the presence of NKT cells. Previously, the expression of CXCL16 was studied in immune cells such as macrophages and dendritic cells. Also, it was reported that nonimmune cells such as smooth muscle cells and keratinocytes expressed CXCL16. In our experiment, we found that CXCL16 was expressed on the damaged glomerular cells, probably mesangial cells, but not on intact glomerular cells, and the development of glomerulopathy recruited NKT cells into affected kidney, where CXCL16 was expressed.

To our knowledge, this is the first demonstration that CD1d-dependent NKT cells lead to the prevention of ecGN, and further studies of the combined use of TCRαβ and CD1d−/− mice should be conducted to delineate the functional diversities of NKT cells in vivo. We believe that an understanding of the way in which these cells work could have therapeutic implications for the treatment of human GN.

CONCISE METHODS

Experimental Animals

Male C57BL/6 (B6; approximately 7 to 8 wk old) mice were purchased from Orient Company (Seoul, Korea). CD1d−/− mice were purchased from Jackson Laboratories (Bar Harbor, ME) and backcrossed to C57BL/6 background for 10 generations (B6.CD1d−/−). All of the animal experiments were performed under the approval of the Institutional Animal Care and Use Committee of the Clinical Research Institute at Seoul National University Hospital and according to the Guidelines for the Care and Use of Laboratory Animals of the National Research Council.

Induction of ecGN

Anti-GBM Ab was prepared from the serum of a rabbit immunized against homogenized murine renal cortex in complete Freund’s adjuvant (Sigma, St. Louis, MO). GN was initiated by the intravenous injection of 3 mg of rabbit anti-GBM Ab into 8- to 10-wk-old male C57BL/6 or B6.CD1d−/− mice as detailed in online data supplements.

Adoptive Transfer of Hepatic NKT Cells

For reconstitution of NKT cells, hepatic mononuclear cells from B6 mice were prepared as detailed in online data supplements.

Quantitative Real-Time PCR

Renal tissues were harvested from mice 7 d after disease induction, and the cytokine expression profile was assayed with real-time PCR as detailed in online data supplements.

Histologic Analysis

For assessment of their light microscopic appearance, 4-μm paraffin sections were stained with periodic acid-Schiff reagent. For grading the induced GN, the numbers of glomeruli forming crescent were counted in a blinded manner. A minimum of 50 glomeruli per mouse kidney were evaluated, and the mean value was used as representative for mouse (see online data supplements).

Western Blot Analysis

Kidneys were harvest at days 7 after induction of ecGN. Western immunoblot analysis of kidney was performed using the primary Ab against to phosphorylated p65, 1xBa, TGF-β1, and β-actin to show specificity to their respective antigens as detailed in online data supplements.

Confocal Microscopic Examination

Confocal microscopy was performed by using a LSM510 META laser confocal microscope (Carl Zeiss, Jena, Germany), as described in online data supplements.

Mesangial Cell Proliferation Assay

See online data supplements.

Cytokine Array (Bio-Plex Cytokine Assay)

Mesangial cells were co-cultured with NKT hybridoma cell (5 × 10^5 well; DN32.D3; ATCC, Manassas, VA). NKT cell was activated by α-GalCer (200 ng/ml), and supernatants were harvested after 16 h of culture. For blocking assay, cells were incubated with an anti-CXCL16 neutralizing antibody (R&D Systems, Minneapolis, MN) for 1 h at 37°C before addition of α-GalCer. Supernatants were then assayed for cytokines using a multiplex cytokine bead array system (Bio-Plex; Bio-Rad, Hercules, CA) according to the manufacturer’s instructions (see online data supplements).

Statistical Analysis

The results are expressed as means ± SD or means ± SEM where appropriate. Statistical analysis was performed using GraphPad Prism 5.0 (GraphPad Software, San Diego, CA). For comparison of more than two groups, the one-way ANOVA statistical analysis using Tukey test was performed. P < 0.05 was used to indicate a statistically significant difference.

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DISCLOSURES

None.

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