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Original Article

Interleukin-17 Enhances Germinal Center Formation and Immunoglobulin G1 Production in Mice

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Objective. Interleukin (IL)-17 is a pro-inflammatory cytokine that has pleiotropic effects on multiple target cells and thereby contributes to the development of immune-mediated inflammatory disorders. However, the role of IL-17 in the humoral immune response has not been clearly elucidated. **Methods.** Mice deficient in IL-17A (IL-17A knockout [KO] mice) and wild type (WT) C57BL/6 mice were compared. Distinct B cell (mature/precursor and marginal zone/follicular) and plasma cell populations were compared using fluorescence-activated cell sorting (FACS) and confocal immunostaining. Immunoglobulin production was assessed by enzyme-linked immunosorbent assay. **Results.** There was no difference in B cell and plasma cell populations between IL-17A KO and WT mice. However, after T cell-dependent antigen challenge, IL-17A KO mice produced lower levels of immunoglobulin (Ig)G1 than wild-type animals. IL-17A KO mice also showed reduced germinal center (GC) formation and lower expression of activation-induced cytidine deaminase, the essential enzyme for class switch recombination (CSR). IL-17 had no effect on the proliferation or survival of naïve B cells in in vitro functional studies. However, IL-17 treatment promoted naïve B cell differentiation into plasma cells in synergy with IL-4, although IL-17 alone had no effect. **Conclusion.** Our findings suggest that IL-17 contributes to the humoral immune response by enhancing GC formation, CSR to IgG1, and plasma cell differentiation in synergy with IL-4. **(J Rheum Dis 2017;24:271-278)**

Key Words. Interleukin-17, B cell, Germinal center

INTRODUCTION

Interleukin (IL)-17 is a pro-inflammatory cytokine that affects various kinds of target cells expressing the IL-17 receptor (R). The IL-17 cytokine family has six members, IL-17A～F, among which, the biological function of IL-17A is best understood. IL-17A, commonly referred to as IL-17, is the representative cytokine in the family that supports pro-inflammatory response. IL-17F, which shares 50% sequence homology with IL-17A, is also known to have a similar pro-inflammatory function. Recent advances in the understanding of the function of IL-17 has revealed its contribution to the development of various immune-mediated inflammatory disorders [1]. Particularly, it has been shown to play a role in autoimmune diseases such as rheumatoid arthritis (RA) [2], psoriasis [3], multiple sclerosis [4,5] and is known to be central to the pathogenesis of these diseases. Indeed, the deficiency or blockade of IL-17 in various animal models of autoimmune diseases led to amelioration of the disease [6,7] and several monoclonal antibodies against IL-17 are in clinical trials [8]. Deficiency or blockade of IL-17 in animal models of autoimmune diseases was associated with reduced production of autoantibodies [6,7]. Autoantibody production is one of the hallmarks of autoimmune diseases, and B cell depleting therapy has shown efficacy in RA [9] and anti-neutrophil cytoplasmic antibody-associated vasculitis [10]. Therefore, the role of

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IL-17 in antibody production in the humoral immune response is worth investigating for proper treatment of autoimmune diseases; however, this has not been investigated in significant detail.

Xie and colleagues [11,12] reported the first evidence that IL-17 affected antibody production by B cells in an autoimmune BXD2 mouse model. The authors argued that IL-17 induced regulator of G-protein signaling proteins, which suppressed migration, and consequently stabilized germinal center (GC) B cells to elicit proper GC reaction [11,12]. In line with this, it was reported that Th17 cells transferred into wild type (WT) C57BL/6 mice induced GC formation, which was abrogated in IL-17 RA knockout (KO) mice [13]. In contrast, a recent study by Corneth et al. [14] demonstrated that GC formation was not affected in collagen-induced arthritis (CIA) IL-17RA KO mice; however, the mice had fewer plasma cells and produced lower levels of immunoglobulin (Ig)G2c antibody than WT controls. Based on these previous observations, we sought to investigate the influence of IL-17 on B cells and immunoglobulin production after T cell-dependent antigen challenge using IL-17 KO mice. Here, we demonstrate that IL-17 KO mice have normal B cell development; however, after chicken γ-globulin haptenated with 4-hydroxy-3-nitrophenylacetyl (NP-CGG) challenge, they showed reduced germinal center formation and activation induced cytidine deaminase (AID) expression. They also produced lower levels of NP-specific IgG1 than wild-type animals.

MATERIALS AND METHODS

Animals and immunization

IL-17 KO mice were kindly provided by Prof. Yoichiro Iwakura (Center for Experimental Medicine, Institute of Medical Science, University of Tokyo, Tokyo, Japan). The experimental mice were housed in filter-top cages, with water and food provided ad libitum. All animal research procedures were performed in accordance with the Laboratory Animals Welfare Act, the Guide for the Care and Use of Laboratory Animals, and the Guidelines and Policies for Rodent Experiment provided by the IACUC (Institutional Animal Care and Use Committee) in the School of Medicine, The Catholic University of Korea (no. CUMC-2008-0091-01). Mice were immunized intraperitoneally with 100 μg NP-CGG (Biosearch Technologies, Petaluma, CA, USA) emulsified in complete Freund's adjuvant (Difco, Detroit, MI, USA). In some experiments, mice were boosted intraperitoneally with NP-CGG (100 μg in phosphate buffered saline [PBS]) on day 14 post initial immunization.

Measurement of NP-specific antibodies

The serum levels of NP-specific immunoglobulin were measured by enzyme-linked immunosorbent assay (ELISA). First, microtiter plates were coated with NP (30 μg/mL) or bovine serum albumin (BSA) (50 μg/mL) in PBS at 4°C overnight, followed by a blocking step for 30 minutes at room temperature. Serum samples were then diluted 1,000- to 100,000-fold in Tris-buffered saline (pH 8.0) containing 1% BSA and 0.5% Tween-20, and incubated in the microtiter plates for 1 hour, after which the plates were washed five times. The concentrations of IgG, IgG2a, IgG1, and IgM were measured using mouse ELISA Quantitation Kits (Bethyl Laboratories, Montgomery, TX, USA). The absorbance values were determined at 450 nm using an ELISA microplate reader.

Analysis B cell populations by flow cytometry

Spleens of eight-week old mice were collected for cell preparation and washed twice with PBS. They were then minced and red blood cells were lysed with 0.83% ammonium chloride. The cells were filtered through a cell strainer and washed in RPMI 1640 medium. For staining, 1×10^6 cells were washed twice with PBS and resuspended in 100 μL of fluorescence-activated cell sorting (FACS) buffer (0.002% sodium azide and 0.2% BSA in Dulbecco's PBS). After washing, the cells were stained in a total volume of 200 μL with 0.5 μg of a combination of monoclonal antibodies (mAbs). The mAbs used were FITC-conjugated anti-IgD (eBioscience, San Diego, CA, USA), biotin anti-IgM, biotin anti-CD138 (BD Pharmingen, San Diego, CA, USA), biotin anti-CD21 (eBioscience), PE-conjugated anti-CD23 (eBioscience), APC-conjugated anti-B220 (eBioscience) and Percp Conjugated Streptavidin (eBioscience). Subsequently, cells were analyzed using a FACS Calibur flow cytometer and CellQuest software (BD Biosciences, San Jose, CA, USA).

In a specific subset of experiments, splenocytes of NP-CGG immunized mice or resting B cells for plasma differentiation were isolated and harvested for staining. The cells were stained in a total volume of 200 μL with 0.5 μg of a combination of mAbs. The mAbs used were APC-conjugated anti-mouse B220, Percp-conjugated anti-mouse CD19, and FITC-conjugated anti-mouse IgG1 (all purchased from eBioscience). Subsequently, cells

were analyzed using a FACS Calibur flow cytometer and CellQuest software (BD Biosciences).

Confocal staining

Spleens from mice were collected, embedded in Frozen Tissue Media (optimal cutting temperature compound) and snap-frozen in liquid nitrogen. Frozen sections (7 mm thick) were fixed in acetone for 15 minutes and dried in air after sections were blocked with 10% goat serum for 30 minutes at room temperature. Tissue sections were then stained using directly labeled antibodies: FITC-anti-GL-7 (BD Pharmingen), APC-anti-CD4 (eBioscience), PE-anti-CD138, Biotin-anti-AID (eBioscience), Biotin-anti-IgG1 (BD Pharmingen), and Streptavidin anti-cy-3 suspended in PBS (pH 7.5). Sections were incubated overnight at 4°C and confocal images were acquired using a LSM 510 confocal microscope (Carl Zeiss, Oberkochen, Germany) at ×200 or ×400 magnification.

Plasma cell differentiation

Resting B-lymphocytes were isolated from the spleen of untreated 6-week old mice by magnetic depletion of all other immune cells with CD43-specific magnetic microbeads (Miltenyi Biotec, Bergisch Gladbach, Germany). The cells were then plated in 24-well plates (Corning, NY, USA) at a concentration of 1×10^6 cells/well. For activation of splenic resting B cells, cells were stimulated 5 μg/mL of anti-IgM with IL-4 (5 ng/mL, R&D system) and/or IL-17 (10 ng/mL, R&D system) for 5 days.

Reverse transcription-polymerase chain reaction analysis of AID mRNA expression

Total mRNA was extracted using RNAzol B (Biotecx Laboratories, Houston, TX, USA) according to the manufacturer's instructions. The mRNA (2 μg) was reverse transcribed at 42°C using the SuperScript Reverse Transcription system (TaKaRa, Shiga, Japan). Polymerase chain reaction (PCR) amplification of cDNA aliquots was performed by adding 2.5 mM dNTPs, 2.5 U of TaqDNA polymerase (TaKaRa), and 0.25 μM sense and antisense primers. The reactions were processed in a DNA thermal cycler (Perkin Elmer Cetus, Norwalk, CT, USA) through 30 cycles at 94°C for 30 s, 62°C for 30 s, and 72°C for 30 s. PCR products were run on a 2.5% agarose gel and stained with ethidium bromide. The results are expressed as the ratio of target PCR product relative to β-actin product. Specific amplification was performed using the following primers: mice AID sense, 5'-GCC ACC TTC GCA ACA AGT CT-3' and antisense, 5'-CCG GGC ACA GTC ATA GCA C-3'; mice β-actin sense, 5'-GAA ATC GTG CGT GAC ATC AAA G-3' and antisense, 5'-TGT AGT TTC ATG GAT GCC ACA G-3'.

Statistical analysis

Statistical analyses were performed using the GraphPad Prism 4.0 software (GraphPad Software Inc., San Diego, CA, USA). Data were compared using the Mann-Whitney U test or two-factor analysis of variance with Bonferroni's post-test. A value of $p<0.05$ was taken to indicate statistical significance.

RESULTS

Comparison of B cell populations in IL-17 knockout and wild type mice

First, we investigated whether any differences in the B cell populations of IL-17 KO and WT mice existed. Total splenocytes obtained from 8-week old IL-17 KO and WT mice were analyzed for expression of the B-cell marker B220, and among the $B220^+$ cells, various B cell subpopulations were compared. As shown in Figure 1, the IgD^+IgM^- mature B cell and IgD^-IgM^- precursor B cell populations of IL-17 KO and WT mice were comparable. The frequency of marginal zone B cells and follicular B cells was also comparable between WT and IL-17 KO mice. There was also no difference in the frequency of plasma cells. Collectively, our data suggest that IL-17 deficiency does not influence spontaneous B cell development or plasma cell differentiation.

IgG1 production was reduced in IL-17 knockout mice

Next, we investigated whether IL-17 influences antigen-specific immunoglobulin production. Two weeks after NP-CGG immunization, antigen-specific IgG production in IL-17 KO and WT mice was compared. Figure 2A shows the serum level of IgG measured by ELISA. There was no difference in the level of total IgG, IgG2a, or IgM; however, the level of IgG1 was significantly higher in WT mice than in IL-17 KO mice. In agreement with this finding, FACS analysis determined that the frequency of $B220^+IgG1^+$ cells was reduced in IL-17 KO mice compared with the WT (Figure 2B). Our data suggest that IL-17 may enhance antigen-specific IgG1 production in vivo.

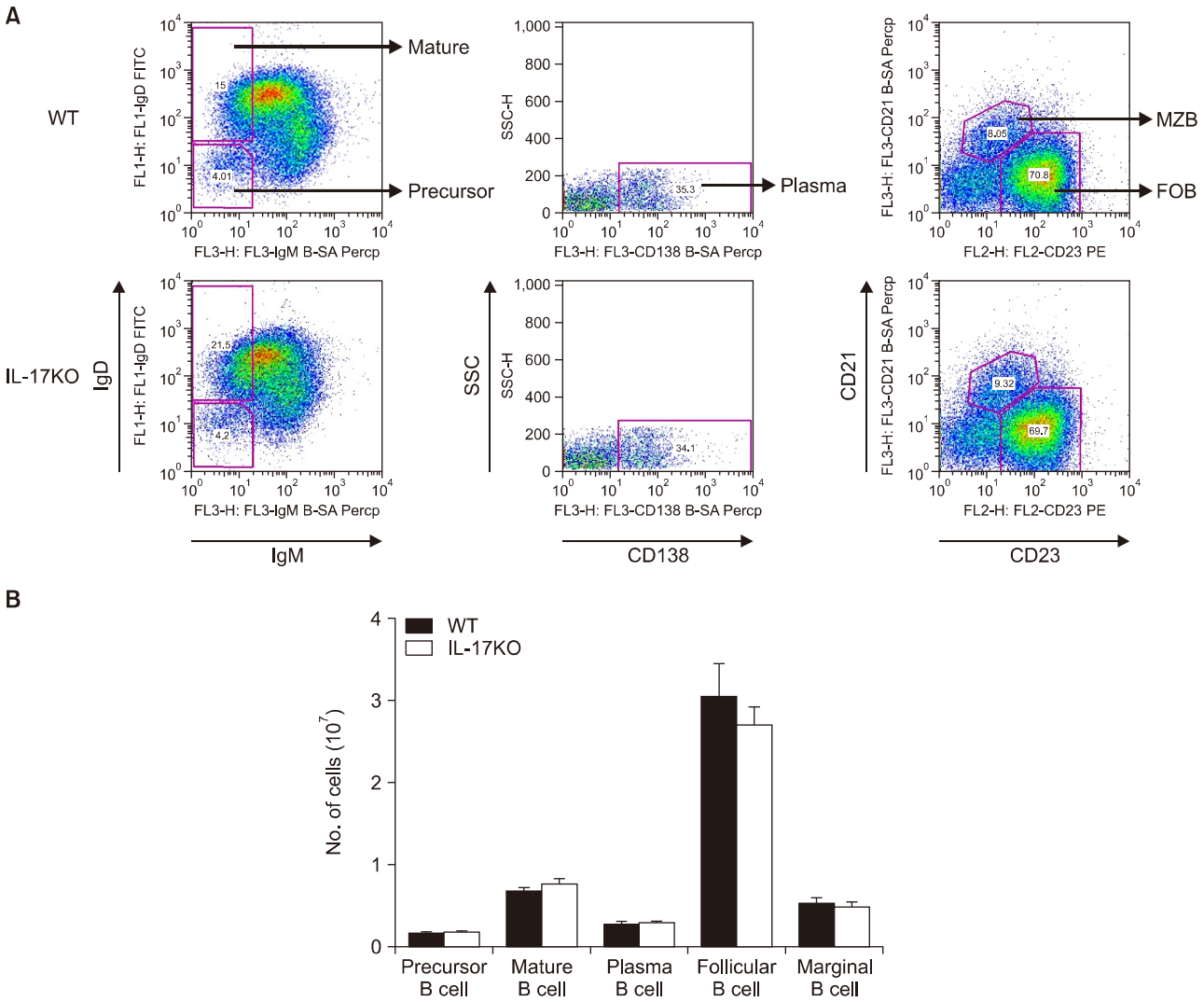

Figure 1. Comparison of the B cell populations of wild type (WT) and interleukin (IL)-17 knockout (KO) mice. Various B cell subpopulations were compared using FACS analysis. (A) Amongst the $B220^+$ B cells, the subpopulation of precursor B cells (IgD^- IgM^-), mature B cells (IgD^+ IgM^-) (left), plasma B cells ($CD138^+$) (middle), follicular B (FOB) cells ($CD21^{low}$ $CD23^+$), and marginal zone B (MZB) cells ($CD21^+$ $CD23^{low}$) (right) were compared. The top panel shows WT and the bottom panel shows IL-17 KO. (B) The number of cells measured by FACS. Data are presented as mean ± standard error of the mean. Ig: immunoglobulin, SSC: side scatter.

Reduced number of germinal center B cells and expression of activation-induced cytidine deaminase in IL-17 knockout mice

To elucidate the mechanism involved in reduced IgG1 production with IL-17 deficiency, we hypothesized that the germinal center reaction was suppressed in IL-17 KO mice. Two weeks after immunization of NP-CGG, spleens from IL-17 KO and WT mice were isolated and immunostained for GC associated markers. As shown in Figure 3A, the number of GCs was lower in IL-17 KO mice. Furthermore, IgG1 expressing GC B cells were less frequently observed in the spleens of IL-17 KO mice (Figure 3B). In addition to the reduced number of GCs, the expression of AID, which is critical for class switch recombination (CSR), was also reduced in IL-17 KO mice. AID-expressing germinal center B cells were less frequently observed by confocal immunostaining (Figure 4A) and mRNA expression of AID in total splenocytes was lower in IL-17 KO mice than in WT mice (Figure 4B).

IL-17 enhances plasma cell differentiation in synergy with IL-4

We next investigated whether IL-17 contributes to plasma cell differentiation after antigen challenge. Two weeks

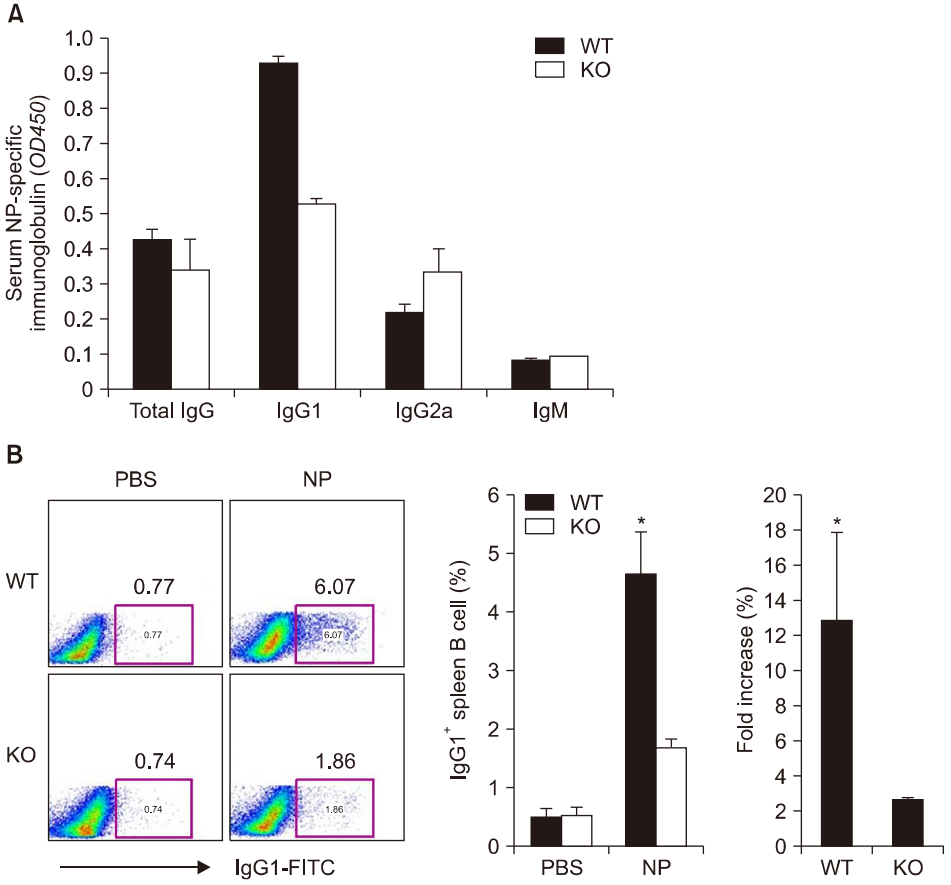

Figure 2. Interleukin (IL)-17 contributes to immunoglobulin (Ig) G1 production in mice. Plasma samples (A) and spleen cells (B) were obtained on day 14-post immunization. (A) The levels of anti-4-hydroxy-3-nitrophenacetyl (NP) immunoglobulin in the plasma were measured by enzyme-linked immunosorbent assay (immunostaining, ×400). (B) The levels of total IgG1 positive splenic B cells were measured by FACS analysis. Data are presented as mean±standard error of the mean. WT: wild type, KO: knockout, AID: activation-induced cytidine deaminase. *p-value<0.05.

after NP-CGG immunization, spleens of IL-17 KO and WT mice were immunostained for $CD138^+$ plasma cells. The results showed that there were fewer plasma cells in IL-17 KO spleens (Figure 5A), suggesting that IL-17 might be involved in plasma cell differentiation. To address this, we isolated $CD43^-$ resting B cells from WT mice, stimulated with anti-IgM antibody, and cultured in the presence or absence of IL-17 or IL-4. Although IL-17 treatment alone failed to enhance plasma cell differentiation, it promoted plasma cell differentiation in synergy with IL-4 (Figure 5B).

DISCUSSION

In the present study, we demonstrate that IL-17 deficiency does not influence spontaneous B cell development by showing comparable B cell populations in IL-17 KO mice and WT mice. However, IL-17 KO mice showed a reduction in the number of GCs and lower levels of IgG1 production after antigen challenge. The expression of AID and the frequency of plasma cells were also reduced compared to WT.

Our results suggest that IL-17 may enhance CSR to IgG1. This was consistent with the previous findings of Patakas et al. [15], which demonstrated that adoptive transfer of Th17 polarized CD4+ T cells allowed higher IgG1 levels than did their Th1 polarized counterpart. In contrast, Mitsdoerffer et al. [13] reported that IL-17 drove B cells to undergo preferential isotype class switching to IgG2a and IgG3 subtypes in a systemic autoimmune disease model (BXD2 mice). The discrepancy between the studies seems to have partly resulted from the use of different experimental settings. As mentioned, the IL-17 cytokine family has six members and each member mediates its function through a distinct surface receptor on target cells. There are 5 receptors, IL-17RA-E, in the IL-17R family, and they form heterodimers with IL-17RA as a common receptor. For example, IL-17 (IL-17A) is recognized by a heterodimer of IL-17RA and IL-17 RC, whereas the receptor for IL-17F consists of IL-17RA and IL-17 RB. To address the potential contribution of IL-17 in the humoral response, we used IL-17 KO mice that only lack IL-17 among the IL-17 cytokine family, whereas Mitsdoerffer et al. [13] used IL-17RA de-

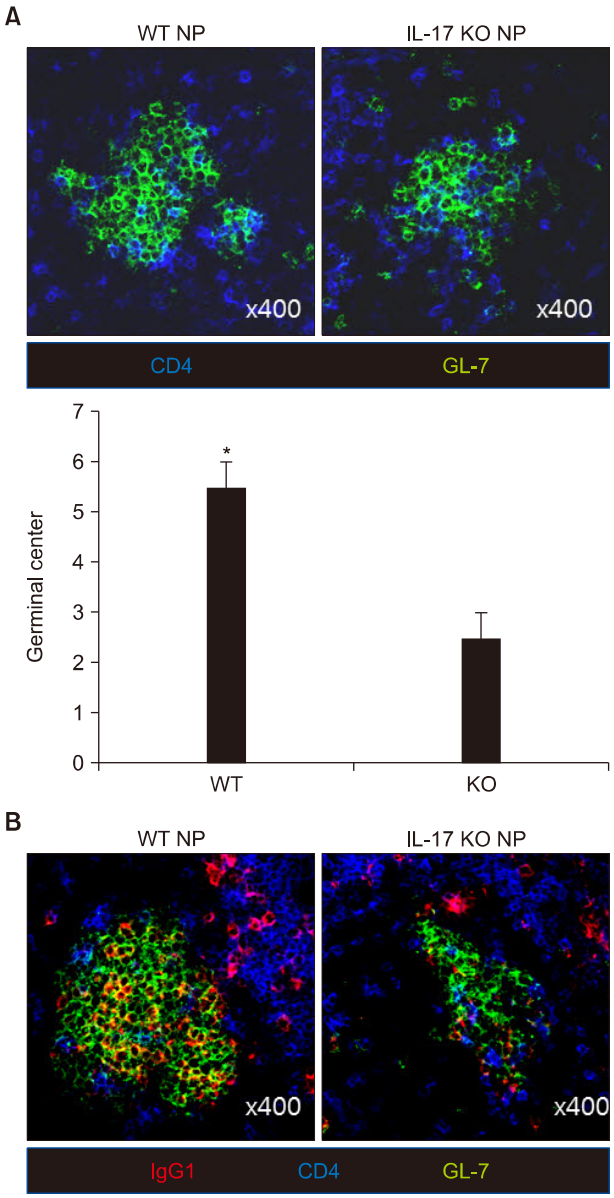

Figure 3. Reduced germinal center formation in interleukin (IL)-17 knockout (KO) mice. Spleen tissue was obtained 14 days post immunization. (A) The number of germinal centers was observed on a cross section field using confocal microscopy (immunostaining, ×400). (B) Immunostaining for immunoglobulin (Ig)G1, CD4, and GL-7 was performed. Data are presented as mean±standard error of the mean. WT: wild type, NP: 4-hydroxy-3-nitrophenacetyl. *p-value<0.05.

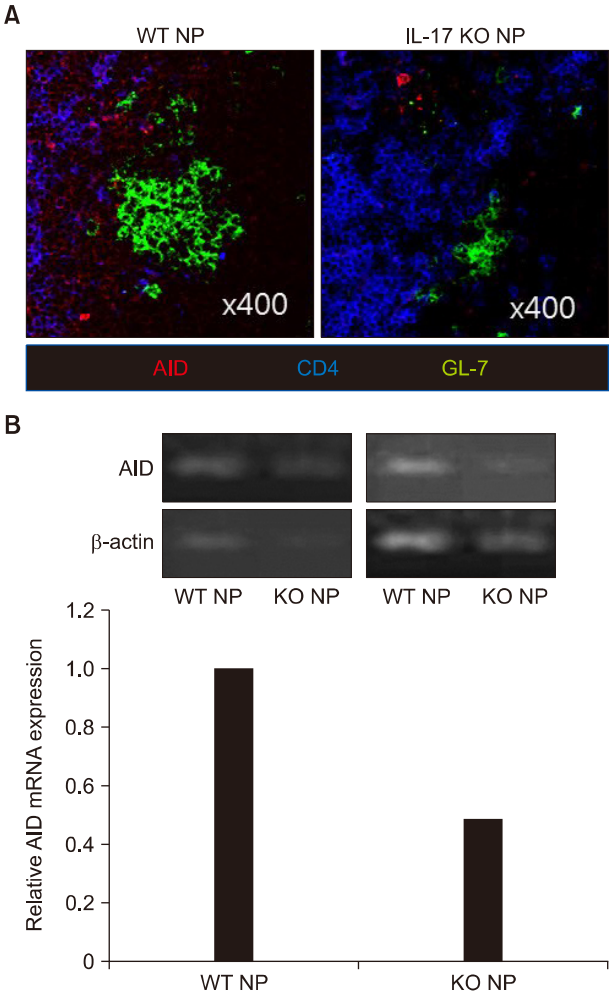

Figure 4. The expression of activation-induced cytidine deaminase (AID) is decreased in the splenocytes of interleukin (IL)-17 knockout (KO) mice. The spleens (A) and splenocytes (B) were obtained on day 14-post immunization. (A) Immunostaining for AID, CD4, and GL-7 was performed. (B) The expression of AID in splenocytes was determined by reverse transcription-polymerase chain reaction. Data are presented as mean±standard error of the mean. Representative data are presented. WT: wild type, NP: 4-hydroxy-3-nitrophenacetyl.

ficient mice. As IL-17RA is a common receptor for other members of the cytokine family, the function of other IL-17 cytokine members can also be affected in IL-17RA deficient mice. Therefore, in the IL-17RA deficient model, signals elicited by other members of the IL-17 cytokine family can be blocked, resulting in a different net effect than is observed with only an IL-17 cytokine KO mouse model. This notion is further supported by Corneth et al. [14] who recently reported the difference between IL-17 and IL-17 RA deficiency in CIA mice.

We demonstrated that the number of GCs was reduced in IL-17 KO mice after antigen challenge, verifying that IL-17 is involved in GC formation as previous studies consistently demonstrated [12,13,15,16]. Although we did not demonstrate the mechanism of this phenomenon, possible mechanisms have been suggested. One explanation is that IL-17 stabilizes GC B cells [16] as well as IL-17RA expressing follicular helper T cells (TFH) to conjugate with B cells, thus sustaining the optimal location of

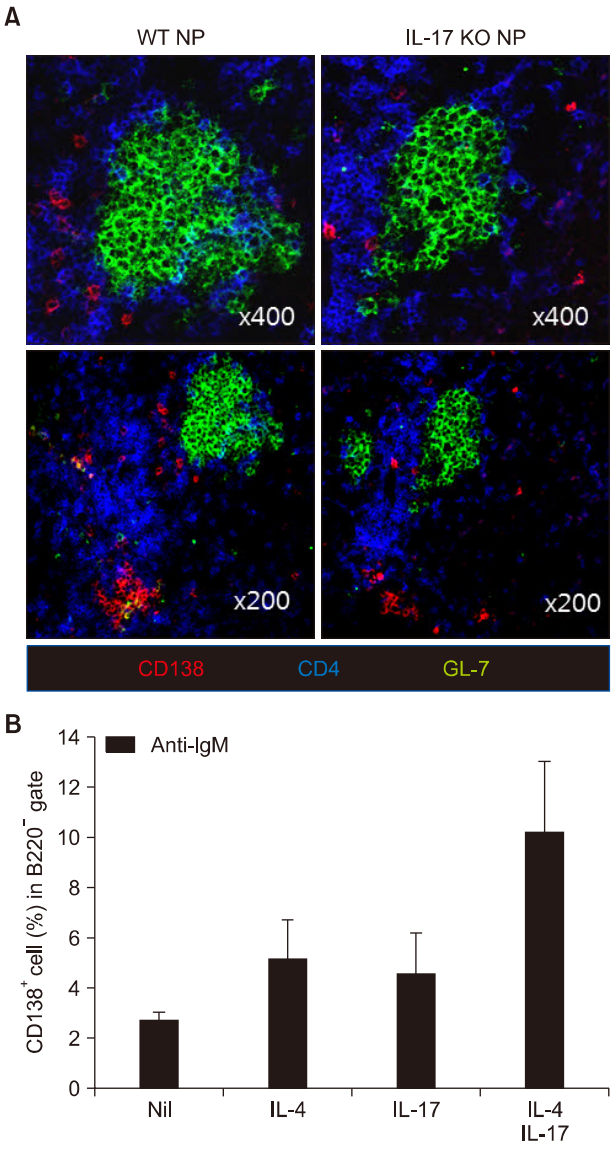

Figure 5. Interleukin (IL)-17 enhances plasma cell differentiation in synergy with IL-4. (A) Spleens were obtained on day 14 after immunization. Immunostaining for CD138, CD4, and GL-7 was performed. (B) Resting B cells were isolated from untreated wild type (WT) mice and cultured with anti-immunoglobulin (Ig)M (5 μg/mL) in the presence or absence of IL-4 (5 ng/mL) and/or IL-17 (10 ng/mL) for 5 days. Cells were harvested and the frequency of $CD138^{+}B220^{-}$ cells was measured using FACS. Data are presented as mean ± standard error of the mean. NP: 4-hydroxy-3-nitrophenacetyl, KO: knockout.

TFH in the GC [12] in autoimmune BXD2 mice. However, it is not clear whether this is the case in only an autoimmune disease setting.

The expression of AID was lower in the splenocytes of IL-17 KO mice after antigen challenge, consistent with the findings of Hsu et al. [16], which demonstrated that AID expression was reduced in IL-17R KO mice. As we analyzed total splenocytes, this does not mean reduced AID expression in B cells specifically. However, considering the critical role of AID in CSR, there might be some links between reduced expression of AID and decreased IgG1 in IL-17 KO mice, although future study to clarify the mechanism is warranted.

Finally, we observed that in the spleen of NP-CGG immunized IL-17 KO mice there was a decrease in the number of plasma cells compared with WT mice, suggesting that IL-17 may enhance plasma cell differentiation. Although treatment of IL-17 alone did not affect plasma cell differentiation in vitro, it enhanced plasma cell differentiation in synergy with IL-4. This suggests that IL-17 may enhance the influence of IL-4 in plasma cell differentiation. It is well known that IL-4 preferentially supports IgG1 production in mice whereas interferon-γ promotes CSR to IgG2a [17]. Thus, the results of reduced IgG1 levels in antigen challenged IL-17 KO mice also support the notion that IL-17 helps the function of IL-4. Future studies addressing this issue are required to elucidate the exact mechanism.

CONCLUSION

In conclusion, our data suggest that IL-17 may contribute to the humoral immune response by enhancing GC formation, CSR to IgG1, and plasma cell differentiation. Targeting IL-17 might be a viable option for treatment of autoimmune diseases as it could regulate aberrant humoral responses.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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