MolecularMedicine

Interleukin-9 Is Associated with Elevated Anti–Double-Stranded DNA Antibodies in Lupus-Prone Mice

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Interleukin (IL)-9, which is produced mainly by $CD4^+$ T cells, is implicated in mast cell-related allergic diseases, although its involvement in systemic lupus erythematosus (SLE) pathogenesis remains unclear. Thus, we investigated the presence of IL-9 in lupus-prone MRL/Mp-lpr/lpr (MRL/lpr) mice and examined the role of IL-9 in lupus pathogenesis. Increased levels of IL-9^+ lymphocytes were detected in the spleens and kidneys of MRL/lpr mice and increased IL-9 levels in the spleen correlated with PNA^+ germinal center (GC) cell expansion. The percentage of $CD4^+$IL-9^+ (Th9) cells was increased in MRL/lpr mice and serum IL-9 levels were elevated and closely related to the production of antibodies against double-stranded DNA (dsDNA). IL-9 appears to promote B-cell proliferation and immunoglobulin production, which could be blocked by inhibition of signal transducer and activator of transcription 3 (STAT3). Treatment with neutralizing anti-IL-9 antibody *in vivo* decreased serum anti-dsDNA-antibody titers and alleviated lupus nephritis in MRL/lpr mice. Our findings indicate expansion of Th9 cells in lupus-prone MRL/lpr mice and the correlation of IL-9 with B-cell proliferation and autoantibody production. These findings suggest that IL-9 is a potential therapeutic target for SLE.

Online address: http://www.molmed.org
doi: 10.2119/molmed.2014.00237

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease in which the body's immune system mistakenly attacks healthy tissue (1). Lupus can affect the skin, joints, kidneys, brain and other organs (1). Loss of B-cell tolerance is the hallmark of SLE, an antibody-mediated chronic autoimmune disease characterized by immune complex deposition that contributes to severe organ damage. However, the precise means by which tolerance is breached in SLE and the underlying mechanisms responsible remain obscure.

Interleukin (IL)-9, a member of the IL-2 cytokine family, is secreted by naive $CD4^+$ T cells in response to transforming growth factor (TGF)-β and IL-4 (2–4). Moreover, IL-9 is a growth factor that stimulates mast cells and T cells and facilitates the $CD4^+$IL-9^+ (Th9) immune response of allergic inflammatory diseases including asthma, allergic rhinitis and atopic dermatitis (5–7). Recent studies have shown that serum IL-9 levels are increased in SLE patients (8). In addition, $CD4^+$IL-9^+ Th9 cells are expanded in active SLE patients (8), but the role of IL-9 in SLE pathogenesis remains unknown.

We and others have shown that T helper 17 (Th17) cells, a lineage of effector $CD4^+$ T cells characterized by IL-17 production, are expanded in SLE patients and that IL-17 is overproduced in active SLE, but decreases after treatment (9–11). Previous studies have demonstrated that Th17-cell–derived IL-17 promotes plasma cell maturation and autoantibody production and plays a key role in the humoral immune response in SLE (12). Intriguingly, IL-9 can induce Th17-cell differentiation and IL-17 production (13); however, whether IL-9 and IL-17 work together to aggravate autoimmune and inflammatory diseases remains unknown. Although IL-9 promotes B-cell activation and IgE production in allergic disease (6,14), it is unclear whether IL-9 also induces autoantibody production in SLE patients.

In this study, we observed $CD4^+$IL-9^+ Th9 cell expansion in lupus-prone MRL/Mp-lpr/lpr (MRL/lpr) mice. In these mice, the increased infiltration of IL-9^+ lymphocytes in the spleen was related to germinal center (GC) formation. Serum IL-9 levels were elevated in MRL/lpr mice along with levels of anti–double-stranded DNA (dsDNA) antibody, which serves as an indicator of

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Submitted November 30, 2014; Accepted for publication April 15, 2015; Published Online (www.molmed.org) April 15, 2015.

autoantibody activity. IL-9 induced B-cell proliferation and immunoglobulin production *in vitro*, but this effect was blocked by signal transducer and activator of transcription 3 (STAT3) inhibition. Administration of neutralizing antibody against IL-9 *in vivo* relieved lupus nephritis in MRL/lpr mice. Further study indicated that IL-9 acts synergistically with IL-17 to promote immunoglobulin production *in vitro* and *in vivo*. Our data indicate that IL-9 is linked to B-cell activation and autoantibody production in lupus and that IL-9 is a potential therapeutic target for SLE.

MATERIALS AND METHODS

Mice

Female MRL/lpr and C57BL/6 mice (3 months old) were purchased from the Shanghai Laboratory Animal Center (Chinese Academy of Sciences) and maintained under pathogen-free conditions. The animal protocol was approved by the Institutional Animal Use Committee of the Shanghai Institute for Biological Sciences. Some experiments were performed as modified methods (15,16). MRL/lpr mice were randomized into two groups containing six mice each and were treated with intraperitoneal (IP) injections of phosphate-buffered saline, anti-IL-9 antibody (100 μg/mouse), or anti-IL-19 antibody (100 μg/mouse) plus anti-IL-17 antibody (100 μg/mouse), (eBioscience, San Diego, CA, USA) once every 4 wks for 12 wks, and gremial center formation and kidney injury was analyzed. All antibodies were obtained from eBioscience. To quantify protein in the urine, we collected the total volume of urine excreted over 24 h and measured urinary protein by enzyme-linked immunosorbent assay (ELISA) (Nanjing Jianchen Bioengineering Company, Nanjing, China).

Cytokine and dsDNA Antibody Detection

ELISA kits were used to evaluate mouse serum levels of IL-9 (eBioscience) and anti-dsDNA antibody (R&D Systems Inc., Minneapolis, MN, USA). Levels of IgM and IgG in supernatants of cultured B cells were also evaluated by ELISA (eBioscience).

Flow Cytometry

To detect splenic Th9 cells, cells from mouse spleens were incubated for 5 h with 50 ng/mL phorbol myristate acetate (PMA) and 750 ng/mL ionomycin in the presence of 20 μg/mL brefeldin A (all from Sigma-Aldrich, Inc., St. Louis, MO, USA). Surface staining with FITC-conjugated anti-CD4 (eBioscience) was performed for 15 min. Cells were resuspended in fixation/permeabilization solution (Invitrogen, [Thermo Fischer Scientific Inc., Waltham, MA, USA]) and intracellular staining with PE-conjugated anti-IL-9 or isotype control antibody was performed according to the manufacturer's protocol (eBioscience). After staining, cells were first gated on $CD4^+$ T cells and then the percentages of $CD4^+IL\text{-}9^+$ cells were analyzed in a $CD4^+$ gate using a FACSCalibur (BD Biosciences, San Jose, CA, USA). Data were analyzed with FlowJo software (FlowJo, Ashland, OR, USA; http://www.flowjo.com/).

Immunohistochemistry

Tissues were processed and stained with hematoxylin and eosin (H&E) and sections were examined and interpreted in a blinded fashion, with grading of the kidneys for glomerular inflammation, proliferation, crescent formation and necrosis. Interstitial changes and vasculitis were also noted. Scores from 0 to 3 were assigned for each of these parameters and then added together to yield a final renal score. For example, glomerular inflammation was graded as follows: 0, normal; 1, few inflammatory cells; 2, moderate inflammation; and 3, severe inflammation. Detailed pathology assessment was performed as described previously (17). Immunohistochemistry on tissue sections was performed as described previously (9), using antibodies against IL-9 (Bioss, Beijing, China) and peanut agglutinin (PNA) (Sigma-Aldrich). $IL\text{-}9^+$ and PNA^+ cells were counted under 400 × magnification and five independent microscopic fields were selected randomly for each sample to ensure that the data were representative and homogeneous.

B-Cell Isolation, Culture Conditions and Differentiation

Mouse naïve B cells were purified by negative selection from MRL/lpr mouse spleens following the manufacturer's instructions for $CD43^+$ cell depletion (Invitrogen [Thermo Fisher Scientific]). Naïve B cells (5×10^5 cells) were stimulated for 3 d with 10 μg/mL lipopolysaccharide (LPS) (Sigma-Aldrich), 1 μg/mL anti-mouse CD40 (eBioscience), 1 μg/mL anti-mouse IgM (eBioscience), or 20 ng/mL mouse IL-9, with or without 20 ng/mL mouse IL-17 (eBioscience). IgM and IgG in the supernatants were detected by ELISA. Cell proliferation was analyzed with (4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) after 2 d stimulation. For some experiments, B-cell cultures were supplemented with 50 μmol/L STAT3 activation inhibitor SPI (BioVision, Milpitas, CA, USA).

RNA Isolation and Real-Time Reverse Transcription-Polymerase Chain Reaction (RT-PCR)

The mRNA expression of *IL-17*, *IL-6*, intercellular adhesion molecule-1 (*ICAM-1*) and vascular cell adhesion molecule-1 (*VCAM-1*) in spleen was analyzed by real-time RT-PCR. Total RNA was purified with TRIzol reagent (Invitrogen [Thermo Fisher Scientific]), cDNAs were synthesized using the Primescript RT Master Mix Perfect Real-time Kit (TaKaRa Bio Inc., Tokyo, Japan) and mRNA expression levels were examined by cDNA amplification using a Bio-Rad iCycler 7500 Optical System (Bio-Rad, Richmond, CA, USA) using a SYBR Premix EX Taq Real-time PCR Master Mix (TaKaRa). The $2^{-\Delta\Delta C_t}$ method was used to normalize target gene transcription to β-actin expression (internal control) to calculate fold-induction of target mRNA. The following primer pairs were used (listed according to each *Mus musculus* gene):

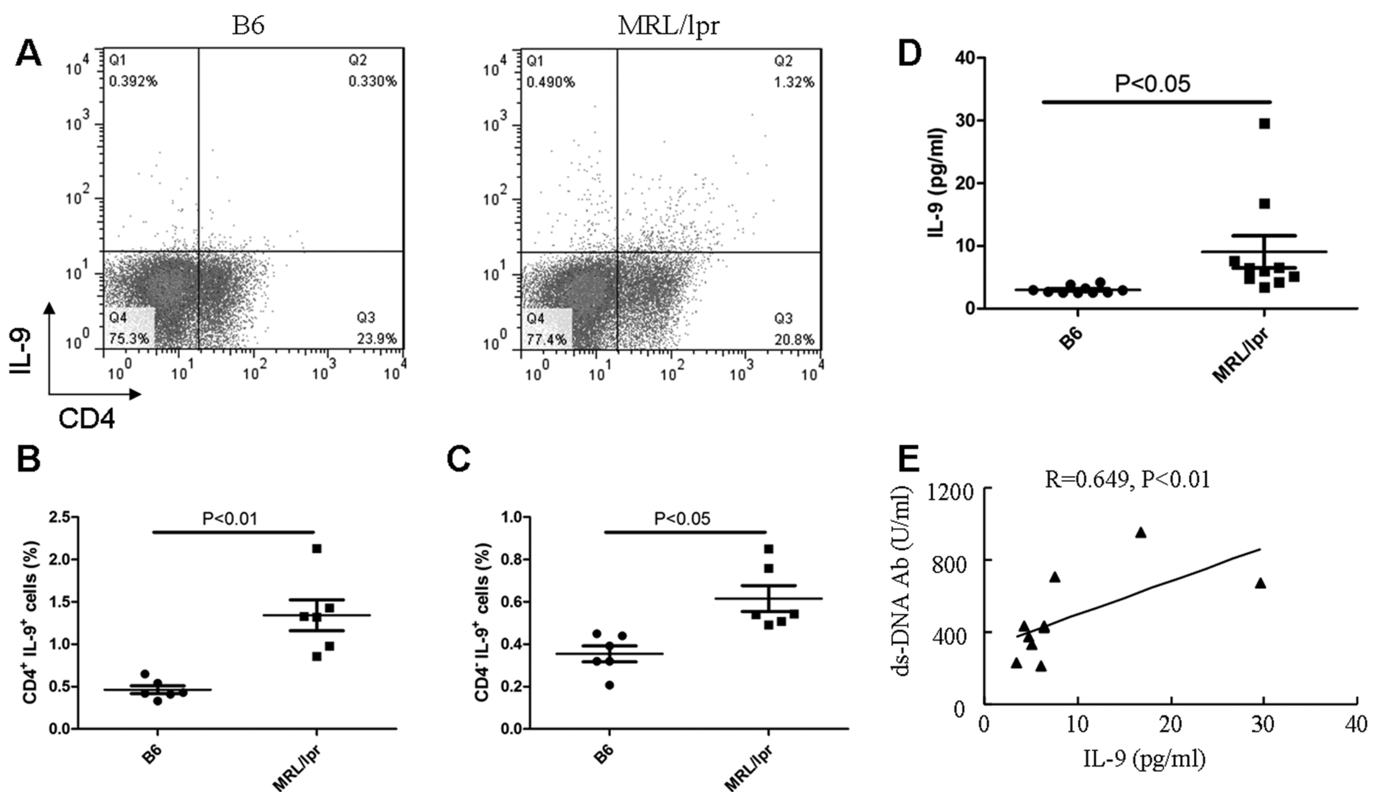

Figure 1. Expansion of Th9 cells in MRL/lpr mice. (A) Splenocytes were isolated from MRL/lpr and B6 mice and stained with anti-CD4 and anti-IL-9 antibodies. $CD4^+IL\text{-}9^+$ cells and $CD4^-IL\text{-}9^+$ cells were analyzed by flow cytometry. (B,C) Percentages of $IL\text{-}9^+$ cells among the $CD4^+$ and $CD4^-$ cell populations in B6 mice and MRL/lpr mice (n = 6 animal/group) were determined. (D) Serum IL-9 levels in B6 and MRL/lpr mice were analyzed by ELISA (n = 6 animals/group). (E) Serum levels of IL-9 and anti-dsDNA antibody were positively correlated in MRL/lpr mice (n = 6).

Mus musculus β-actin: forward, 5′-GACGG CCAGGTCATCACTATTG-3′; reverse, 5′-AGGAAGGCTGGAAAAGAGCC-3′; *Mus musculus IL-17*: forward, 5′-GGGAG AGCTTCATCTGTGTCTC-3′; reverse, 5′-GGTTGACCTTCACATTCTGGA-3′; *Mus musculus IL-6*: forward, 5′-GAGGA TACCACTCCCAACAGACC-3′; reverse, 5′-AAGTGCATCATCGTTGTTCATACA-3′; *Mus musculus ICAM-1*: forward, 5′-CAATTTCTCATGCCGCACAG-3′; reverse, 5′-AGCTGGAAGATCGAA AGTCCG-3′; *Mus musculus VCAM-1*: forward, 5′-TGAACCCAAACAGAG GCAGAGT-3′; reverse, 5′-GGTATCCCAT CACTTGAGCAGG-3′.

Statistical Analyses

Results were expressed as mean ± standard deviation (SD). Statistics were performed using SPSS 13.0 statistical software (SPSS [IBM, Armonk, NY, USA]). Statistical significance was determined by analysis of variance (ANOVA) for comparisons of multiple means, Student *t* test, or Mann–Whitney *U* test. *P* values <0.05 were considered indicative of statistically significant differences between comparator groups. Correlations were determined with Spearman ranking.

All supplementary materials are available online at www.molmed.org.

RESULTS

Expansion of Th9 Cells in Lupus-Prone MRL/lpr Mice

MRL/lpr mice spontaneously develop a severe systemic autoimmune disease similar to human lupus (17). Excessive expansion of inflammatory cells and cytokines is typically detected in lupus; however, the presence and percentage of Th9 cells in MRL/lpr mice remains unknown. We first identified $CD4^+IL\text{-}9^+$ Th9 cells in MRL/lpr mouse spleens (Figure 1A). The percentage of $CD4^+IL\text{-}9^+$ Th9 cells was expanded in spleens of MRL/lpr mice (1. 34 ± 0. 44%) compared with age- and sex-matched B6 mice (0.46 ± 0.11%) (Figure 1B). IL-9 is produced mainly by $CD4^+IL\text{-}9^+$ Th9 cells, although certain other T lymphocytes also have been reported to produce this cytokine (18–20). $CD4^-IL\text{-}9^+$ cells also were detected in spleens of MRL/lpr mice and this population was also expanded in MRL/lpr (0. 62 ± 0.15%) versus B6 mice (0. 35 ± 0.09%) (Figure 1C). In addition, the absolute numbers of $CD4^+IL\text{-}9^+$ Th9 cells and $CD4^-IL\text{-}9^+$ cells were increased in MRL/lpr mice compared with B6 mice (data not shown). Serum IL-9 levels were significantly higher in MRL/lpr mice than in B6 mice (Figure 1D) and serum

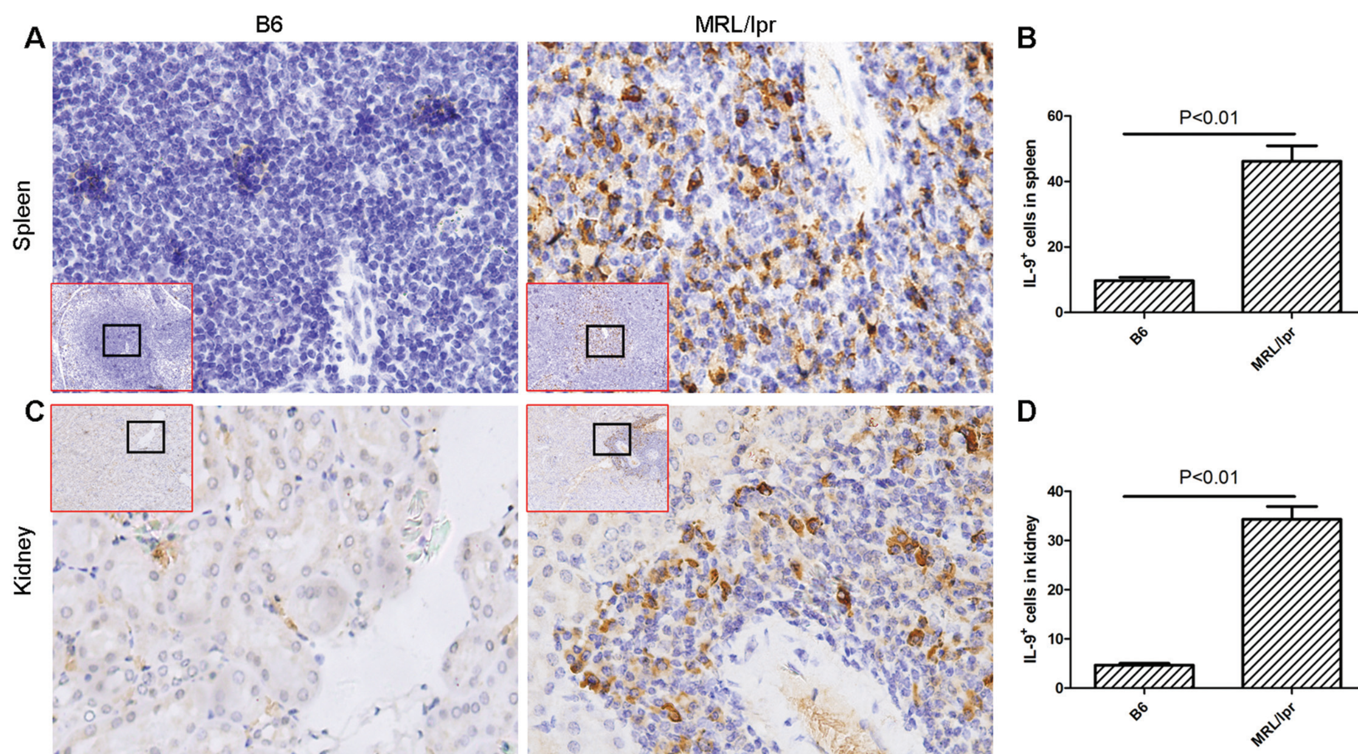

Figure 2. IL-9 protein expression in spleens and kidneys of MRL/lpr mice. (A) IL-9 protein expression in B6 and MRL/lpr mouse spleens was assessed by immunohistochemical staining (100× original magnification). Increased magnification (400×) of the black-bordered box clearly shows the predominance of IL-9$^+$ lymphocytes. (B) The numbers of IL-9$^+$ lymphocytes in spleens of B6 and MRL/lpr mice were determined (n = 6 animals/group). The positive cells and surface area were counted under 400× original magnification and five randomly selected independent microscopic fields were counted for each sample to ensure that the data were representative and homogeneous. (C) IL-9 protein expression in kidneys of B6 and MRL/lpr mice was confirmed by immunohistochemical staining (100× original magnification). Increased magnification (400×) of the black-bordered box shows the predominance of IL-9$^+$ lymphocytes. (D) The numbers of IL-9$^+$ lymphocytes in kidneys of B6 and MRL/lpr mice were determined (n = 6 animals/group). The positive cells and surface area were counted under 400× original magnification and five randomly selected independent microscopic fields were counted for each sample to ensure that the data were representative and homogeneous.

anti-dsDNA-antibody titer correlated positively to serum IL-9 level in MRL/lpr mice (Figure 1E). These data demonstrate that Th9 cells are expanded in lupus-prone MRL/lpr mice and suggest that IL-9 might be related to autoantibody production.

IL-9 Is Related to GC Formation in MRL/lpr Mice

Although IL-9 facilitates B-cell activation and IgE production, the role of IL-9 in the formation of GCs in MRL/lpr mice is not clear. Immunohistochemically detectable IL-9$^+$ cells were present in larger numbers in spleens from MRL/lpr mice than in spleens from B6 mice (Figures 2A, B) (n = 6 animals/group). More IL-9$^+$ cells infiltrated the kidneys of MRL/lpr mice than B6 mice (Figures 2C, D) (n = 6 animals/group). Histological staining showed that PNA$^+$ GC cells were expanded in MRL/lpr mice compared with control B6 mice (Figures 3A, B) and a strong positive correlation between the number of IL-9$^+$ cells and PNA$^+$ GC cells in MRL/lpr mouse spleens was identified (Figure 3C). To further examine the role of IL-9 in the formation of GC cells in lupus-prone MRL/lpr mice, MRL/lpr mice were treated with or without IL-9-neutralizing antibody once every 4 wks for 12 wks. IL-9-neutralizing antibody treatment significantly reduced the formation of GC cells in MRL/lpr mice (Figure 3D). These data imply that increased IL-9 may be related to GC formation in MRL/lpr mouse spleens.

Interleukin-9 in Synergy with IL-17 Promotes Immunoglobulin Production via STAT3 Activation

Although previous data suggested that IL-9 induces IgE production in B cells (21), the mechanism of IL-9-mediated autoantibody production is not clear. IL-9 promoted MRL/lpr mouse-derived B-cell proliferation and IgM and IgG production and IL-17 costimulation synergistically enhanced these responses (Figures 4A, B). In addition, the proliferation and immunoglobulin production from MRL/lpr mouse–derived B cells was higher than that of B6 mouse (Figures S1A–C). Acti-

vation of STAT3 has been reported to be involved in B-cell activation and antibody production (22). To elucidate the role of STAT3 activation in IL-9-induced B-cell activation, isolated naïve B cells were treated with IL-9 combined with IL-17, the data showed that more increased STAT3 gene expression could be detected in B cells from MRL/lpr mouse spleens than in those of B6 mouse (Figures S1D, S2). SPI (a specific STAT3 activation inhibitor) effectively blocked the effects of combined IL-9 and IL-17 on B-cell proliferation and IgM and IgG production (Figures 4C, D). These data demonstrate that IL-17 enhances IL-9-mediated B-cell proliferation and Ig production in MRL/lpr mice by activating STAT3 phosphorylation.

In Vivo Neutralization of IL-9 and IL-17 Relieves Lupus Nephritis Symptoms

Treatment with neutralizing anti-IL-9 antibody alleviated renal injury and decreased serum titers of anti-dsDNA antibody in MRL/lpr mice (Figures 5A, B). When MRL/lpr mice were treated with neutralizing antibodies against both IL-9 and IL-17 once every 4 wks for 12 wks, anti-dsDNA-antibody serum titers were significantly decreased (see Figure 5A). In addition, neutralizing antibodies against both IL-9 and IL-17 could inhibit gene expression of inflammatory cytokines including *IL-6*, *IL-17*, *ICAM-1* and *VCAM-1* (Figure S3). Mice that were not treated with these neutralizing antibodies developed severe nephritis with increased renal inflammatory cell infiltration, whereas treated mice did not develop nephritis and had lower renal scores and levels of urinary protein (Figures 5B–D). These data suggest the potential of IL-9 as a therapeutic target for lupus.

DISCUSSION

IL-9 is primarily recognized as a T-cell–derived factor that is preferentially expressed by Th2 cells. Recent studies revealed a T-cell subset (Th9 cells) that predominantly produces IL-9 and is distinct from the classic Th1, Th2 and Th17 subsets (2–4). Several reports showed that Th9 cells could be involved in the pathogenesis of chronic allergic disorders such as asthma, allergic rhinitis and atopic dermatitis (23,24). Further studies indicated that serum levels of IL-9 are increased in patients with SLE and other autoimmune diseases such as systemic scleroderma (8,25,26). These data suggested that IL-9 may be involved in SLE pathogenesis; however, how IL-9 exerts inflammatory functions during a lupus flare remains unclear.

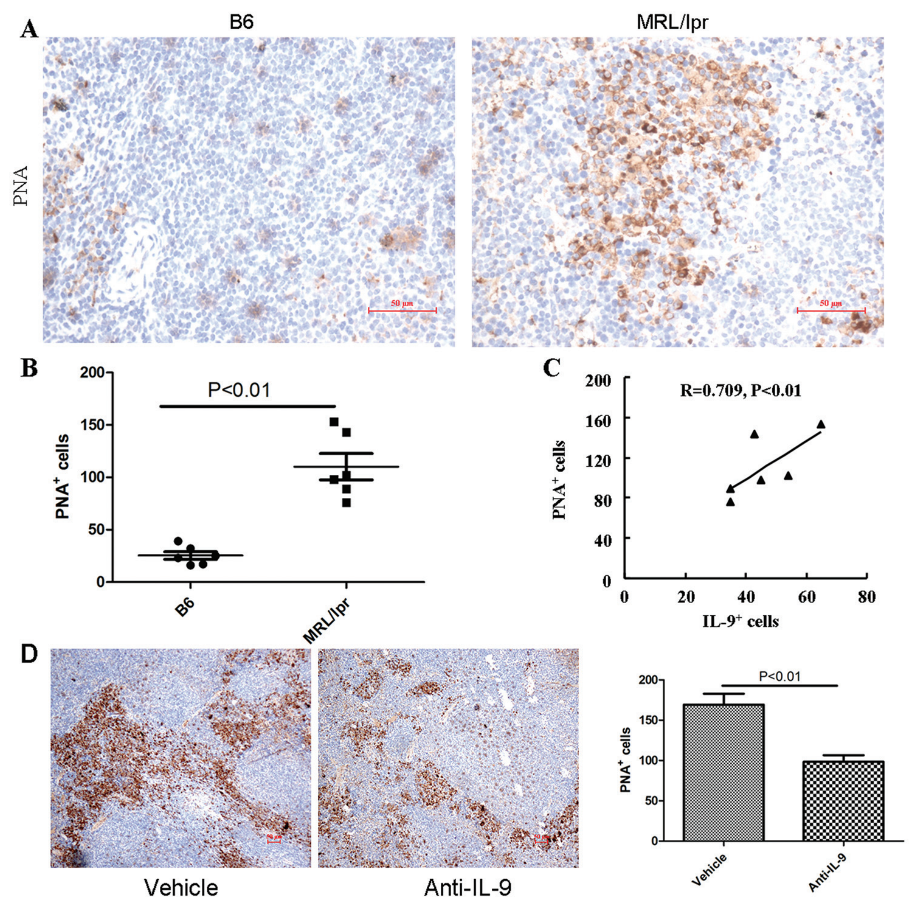

Figure 3. IL-9 is associated with GC formation in spleens of MRL/lpr mice. (A) PNA protein expression in spleens from B6 and MRL/lpr mice was confirmed immunohistochemically. (B) Numbers of PNA⁺ cells in spleens of B6 and MRL/lpr mice (n = 6 animals/group) were determined. Positive cells and surface area were counted under 400× magnification and five randomly selected independent microscopic fields were counted for each sample to ensure that the data were representative and homogeneous. (C) A positive correlation between IL-9⁺ cells and PNA⁺ cells in spleens of MRL/lpr mice was detected (n = 6 animals). (D) MRL/lpr mice were treated with vehicle or IL-9-neutralizing antibody every 4 wks for 12 wks. Numbers of PNA⁺ cells in spleens of MRL/lpr mice were determined (Right, n = 6 animals/group). Positive cells and surface area were counted under 400× magnification and five randomly selected independent microscopic fields were counted for each sample to ensure that the data were representative and homogeneous.

To verify the role of IL-9 in SLE pathogenesis, lupus-prone MRL/lpr mice were analyzed. These MRL/lpr mice spontaneously develop a severe systemic autoimmune disease similar to human lupus and this disease is characterized by severe pan-isotypic hypergammaglobulinemia, autoantibody production, lymphadenopathy and immune complex-associated nephritis (17). Our data demonstrated that greater numbers of IL-9⁺ cells accumulated in the spleens and kidneys of

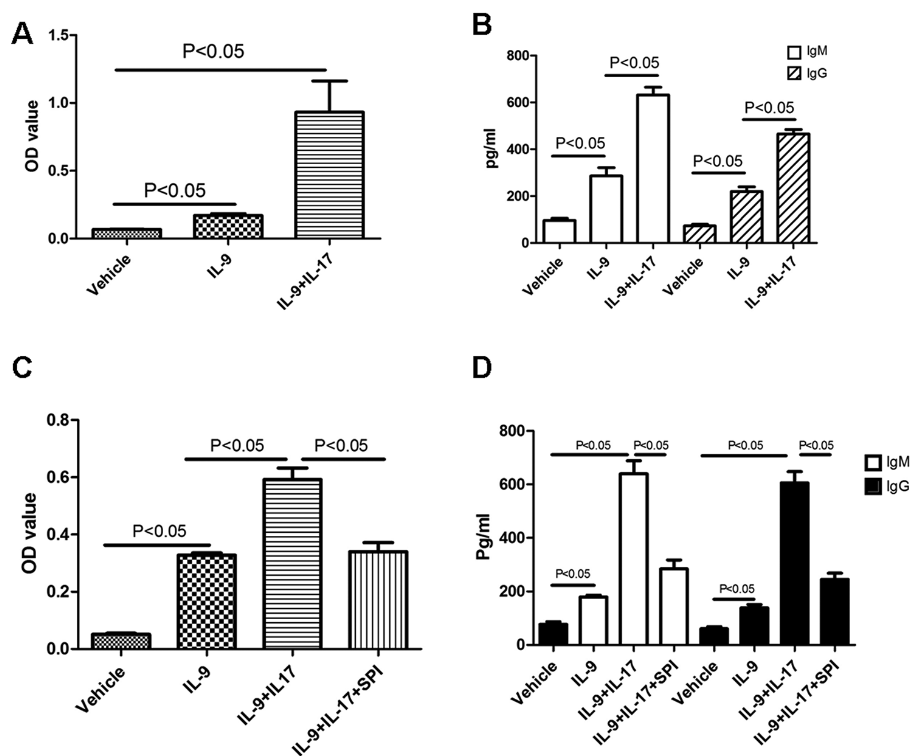

Figure 4. IL-9 induces B-cell proliferation and immunoglobulin production via activation of p-STAT3. (A) Naïve B cells isolated from MRL/lpr mice were cultured with LPS, anti-CD40 or anti-IgM in the presence of IL-9 or IL-9 + IL-17 for 2 d and the proliferation of B cells was analyzed with MTT. (B) Naïve B cells isolated from MRL/lpr mouse spleens were cultured with LPS, anti-CD40 or anti-IgM in the presence of IL-9 ± IL-17 for 3 d, and IgM and IgG secretion into supernatants was measured by ELISA. (C) Naïve B cells isolated from MRL/lpr mouse spleens were cultured with LPS, anti-CD40, anti-IgM or IL-9 + IL-17 in the presence or absence of 50 μmol/L SPI for 48 h, and cell proliferation was analyzed using the MTT assay. (D) Naïve B cells isolated from MRL/lpr mouse spleens were cultured with LPS, anti-CD40, anti-IgM or IL-9 + IL-17 in the presence or absence of SPI for 3 d, and IgM and IgG secretion into supernatants was measured by ELISA. These experiments were performed three times with similar results.

MRL/lpr mice than in spleens and kidneys of B6 mice. Furthermore, $CD4^+IL\text{-}9^+$ Th9 cells were expanded in spleens of MRL/lpr mice compared with those of B6 mice. Interestingly, we noticed that a high percentage of $IL\text{-}9^+$ cells were $CD4^-$ in MRL/lpr mice. Although $CD4^+IL\text{-}9^+$ Th9 cells are a main source of IL-9 during chronic inflammatory responses in mice, other lymphocyte subsets also produce IL-9, including $CD8^+$ T cells, invariant natural killer T (NKT) cells, γδ T cells and Th17 cells (18–20). Thus, we hypothesize that $CD4^-IL\text{-}9^+$ cells are expanded in MRL/lpr mice during severe inflammatory responses, but further studies should be performed to dissect the specific identity, source and function of these $CD4^-IL\text{-}9^+$ cells. Our data from this study, however, imply that $IL\text{-}9^+$ cells are globally expanded in lupus-prone mice.

Our previous work showed that Th17 cells are expanded in SLE patients and that serum IL-17 levels are elevated in SLE patients (9). IL-17 enhances effector B-cell–mediated humoral immunity (12). Previous findings implied that IL-9 induces IgE production in B cells (21). Here, we demonstrated that the number of $IL\text{-}9^+$ cells increased and was closely related to GC formation in spleens of MRL/lpr mice. Serum IL-9 levels were significantly increased in MRL/lpr mice compared with those in B6 mice and were positively correlated with serum dsDNA titers in these animals. These data indicate that IL-9 contributes to B-cell expansion and autoantibody production in lupus.

When naïve B cells were stimulated with IL-9 *in vitro*, IL-9 promoted B-cell proliferation and IgM and IgG production, which were enhanced by concomitant stimulation with IL-17. These data suggest that Th17 and Th9 may act synergistically to promote autoantibody production in SLE. IL-17 and IL-9 activate Janus kinase (JAK)/STAT pathways and phosphorylation of STAT3 in B cells (27,28). We verified that p-STAT3 inhibition by SPI alleviated IL-17- and IL-9-induced B-cell proliferation and IgM/IgG production in B cells from MRL/lpr mice. These findings indicated that STAT3 may play a key role in IL-9-mediated effector B-cell activation and autoantibody production in SLE. Our additional data showed that B-cell proliferation and immunoglobulin production induced by IL-9 were higher in MRL/lpr mice than in B6 mice, which indicated MRL/lpr mouse-derived B cells were more sensitive to IL-9 stimulation. Treatment of MRL/lpr mice with IL-9-neutralizing antibody *in vivo* partly reduce renal injury and serum titer of dsDNA; however, combined treatment with IL-9- and IL-17-neutralizing antibodies significantly relieved lupus nephritis. These data imply that lupus is a complex autoimmune disease characterized by massively expanded effector T-cell populations and increased inflammatory cytokine expression and that single cytokine blockade is not sufficiently effective for the treatment of lupus during disease flares.

CONCLUSION

In summary, our results clearly demonstrate expansion of Th9 cells related to GC formation in the spleens of MRL/lpr mice. In addition, the elevated serum IL-9 levels were related to anti-dsDNA-antibody production in MRL/lpr mice. IL-9 *in vitro* induced B-cell proliferation

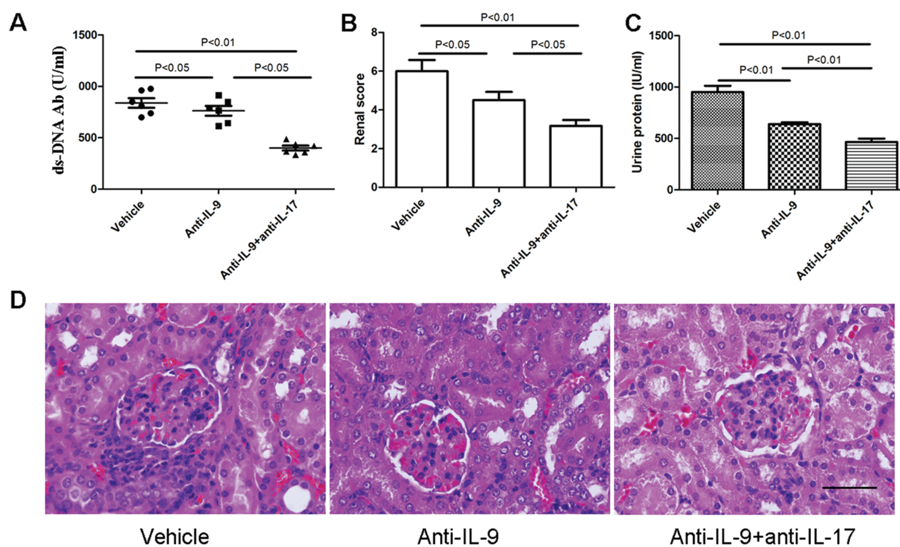

Figure 5. Neutralization of IL-9 and IL-17 can relieve lupus nephritis. (A) MRL/lpr mice were treated with vehicle, IL-9-neutralizing antibody or IL-9- and IL-17-neutralizing antibody every 4 wks for 12 wks. Serum titers of dsDNA antibody were analyzed by ELISA (n = 6 animals/group). (B) The renal score of MRL/lpr mice that were treated with vehicle or IL-9- and IL-17-neutralizing antibody were calculated (n = 6 animals/group). (C) Urinary protein levels were measured by ELISA (n = 6 animals/group). (D) Hematoxylin and eosin staining of the kidneys (100× magnification).

and immunoglobulin production through activation of STAT3. These data imply that IL-9 is linked to B-cell activation and autoantibody production in lupus, suggesting that IL-9 is a potential therapeutic target for SLE.

ACKNOWLEDGMENTS

We thank Haiying Zeng for histology and immunohistochemistry slide preparation. This work was supported by grants from the National Natural Science Foundation of China (nos. 81472874; 8100069; 81401346), Medical Guide Project from Shanghai Municipal Science and Technology (134119a8400), Shanghai Municipal Science and Technology (15ZR1406500) and the Shanghai Young Doctor Cultivation Plan.

DISCLOSURE

The authors declare that they have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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Cite this article as: Yang J, Li Q, Yang X, Li M. (2015) Interleukin-9 is associated with elevated anti–double-stranded DNA antibodies in lupus-prone mice. *Mol. Med*. 21:364–70.