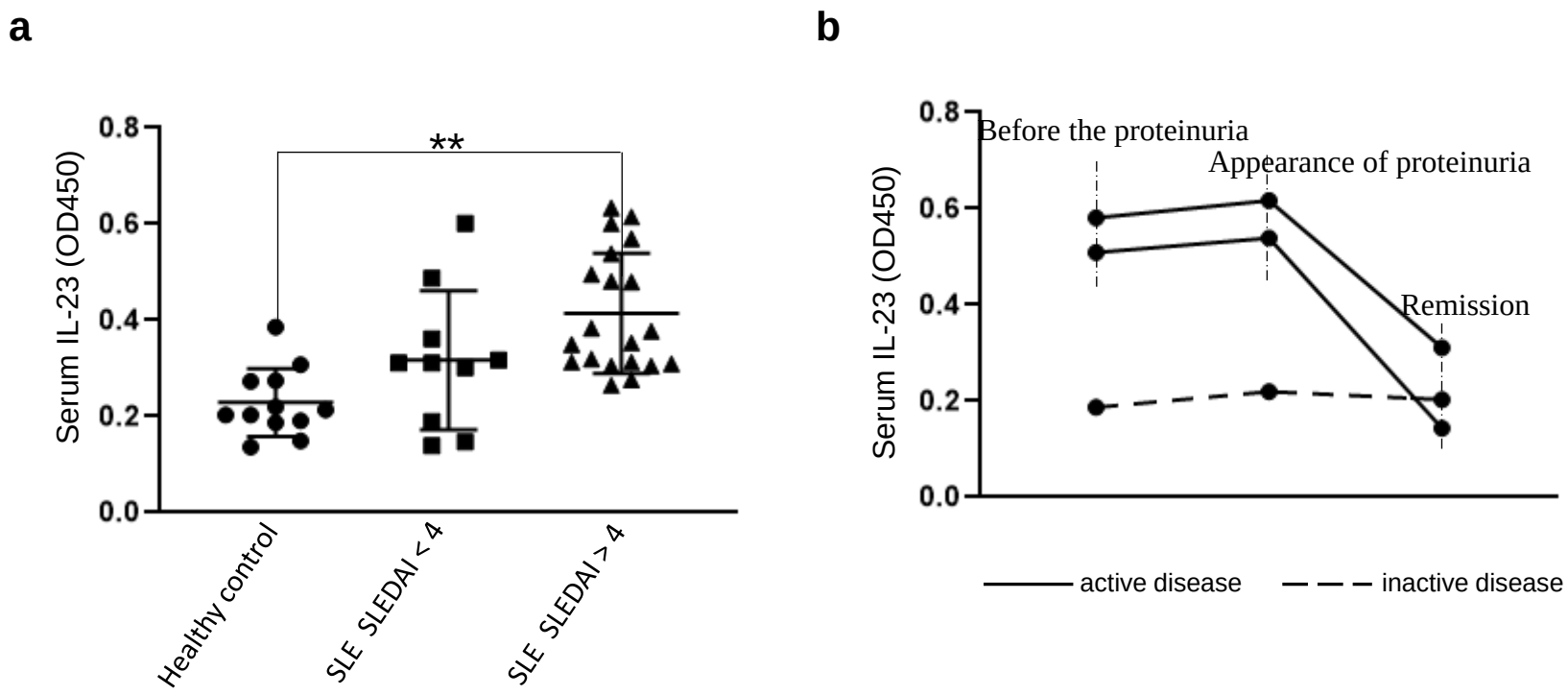
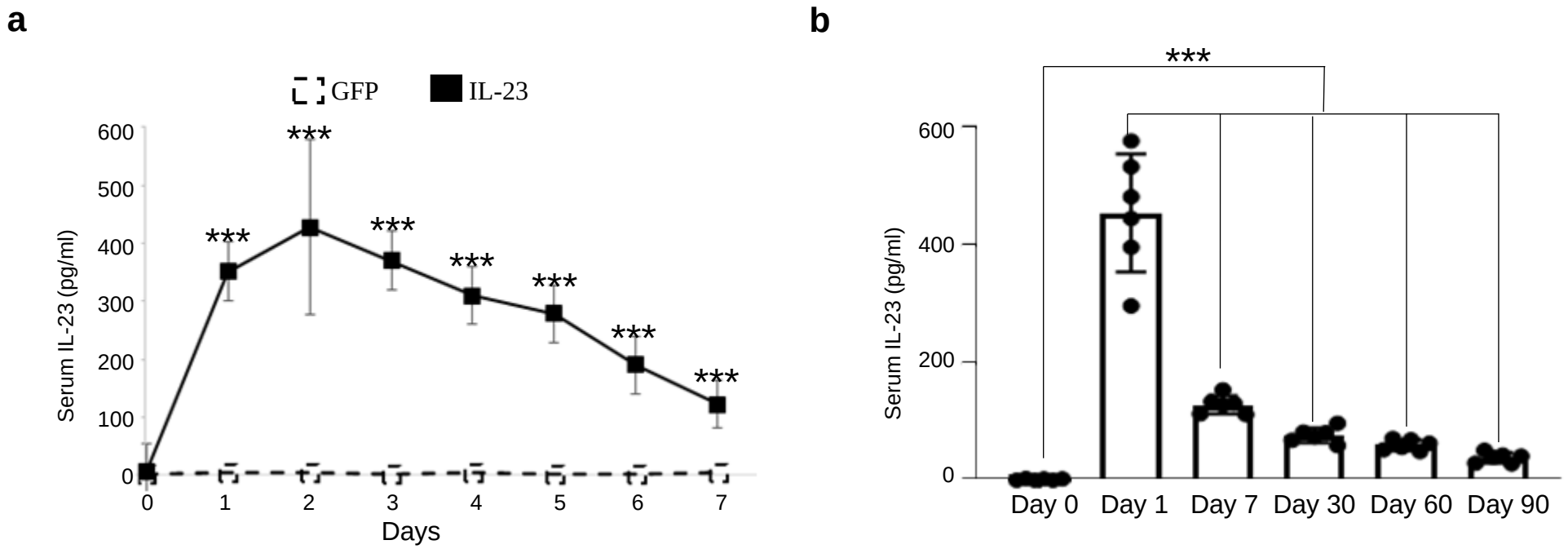


Supplemental Figure 1. Elevation of IL-23 in the sera precedes the appearance of proteinuria in SLE patients.
(a) ELISA analysis of serum IL-23 in the patients from indicated group. SLEDAI: Systemic lupus erythematosus disease activity index. **P < 0.01 vs. control, 2-way ANOVA test.
(b) Serum were collected at three time points (before the appearance of proteinuria, onset of proteinuria and lupus remission) from two patients with active SLE, 1 patient with remission over one continuous year as control. The kinetic curves show the serum IL-23 levels by ELISA.



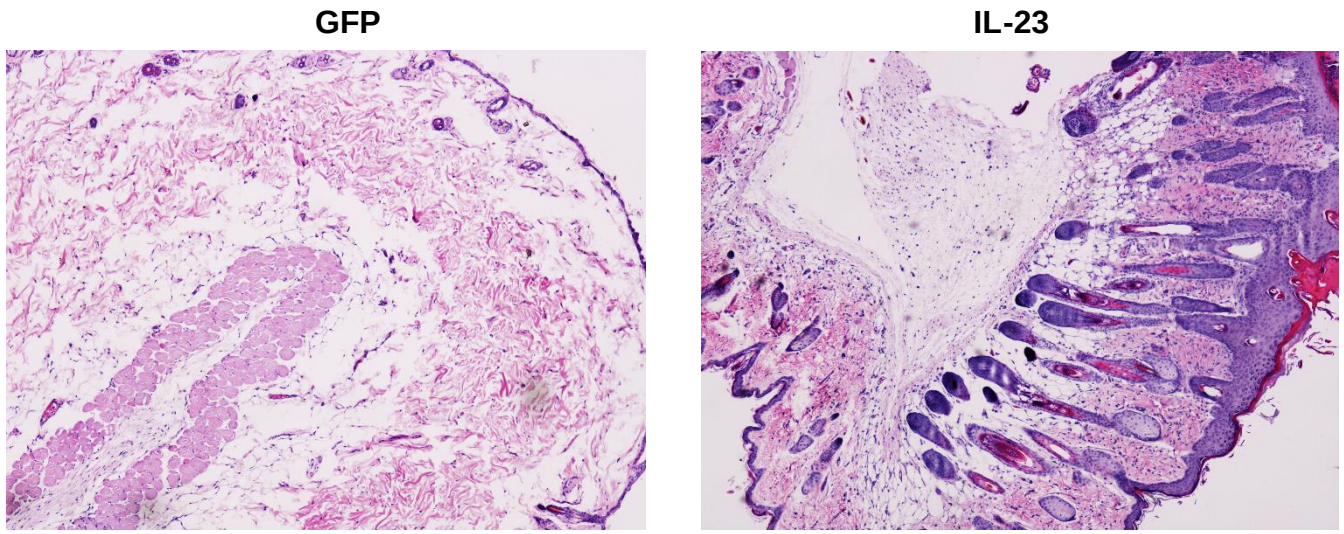
Supplemental Figure 2. Elevated expression of IL-23 in the sera of mice subjected to minicircle administration.

Eight-week-old C57BL/6J mice were i.v. injected with IL-23 or GFP minicircle (MC) and serum were collected for IL-23 ELISA analysis.

a. Serum IL-23 concentration-time curves after indicated minicircle administration.

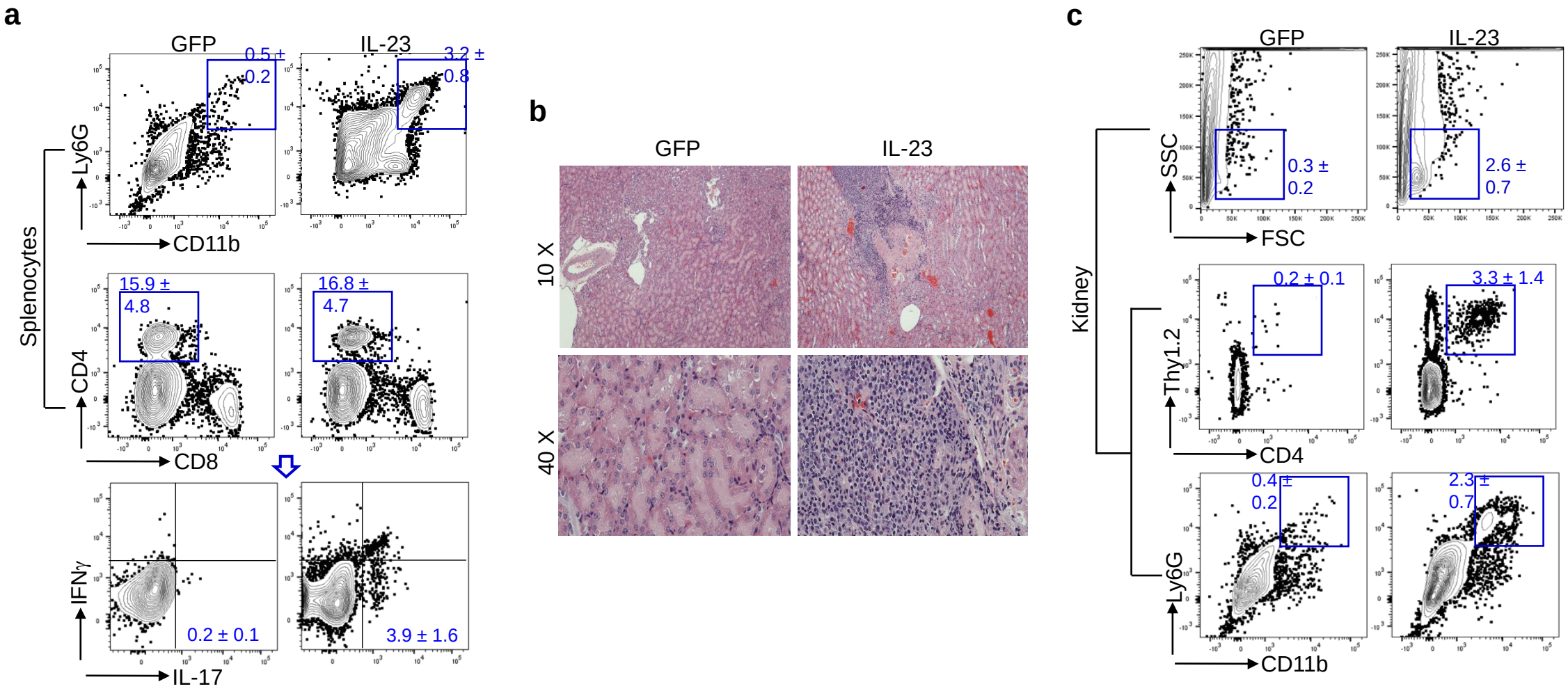
b. b. Bar graphs show the serum titers of IL-23 indicated days after IL-23 MC administration.

n = 5-7 mice per group in each experiment for 2 independent experiments. ***P < 0.005, 2-way ANOVA test;



Supplemental Figure 3. overexpression of IL-23 *in vivo* induces skin lesions.

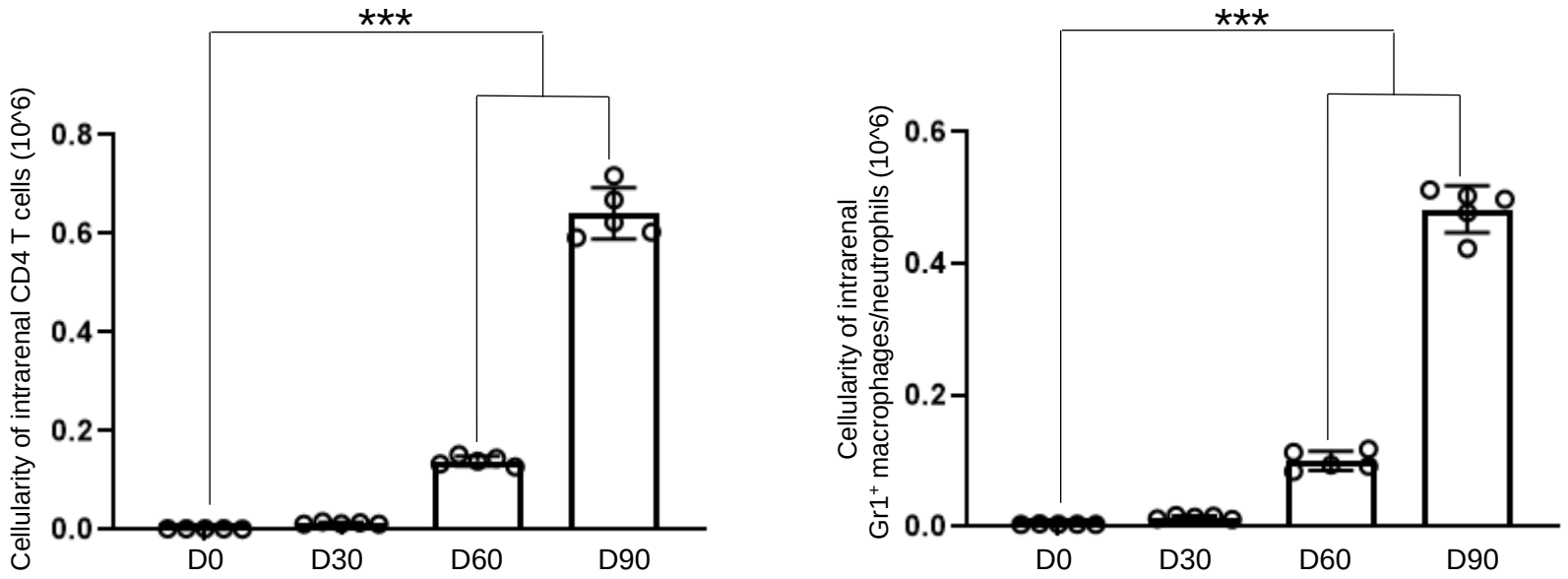
Eight-week-old C57BL/6J mice were i.v. injected with IL-23 or GFP MC for 90 days. Representative Hematoxylin and Eosin stain (H&E) images of skins from indicated mice. n = 5-7 mice per group in each experiment for 2 independent experiments.



Supplemental Figure 4. overexpression of IL-23 *in vivo* instigates kidney inflammation.

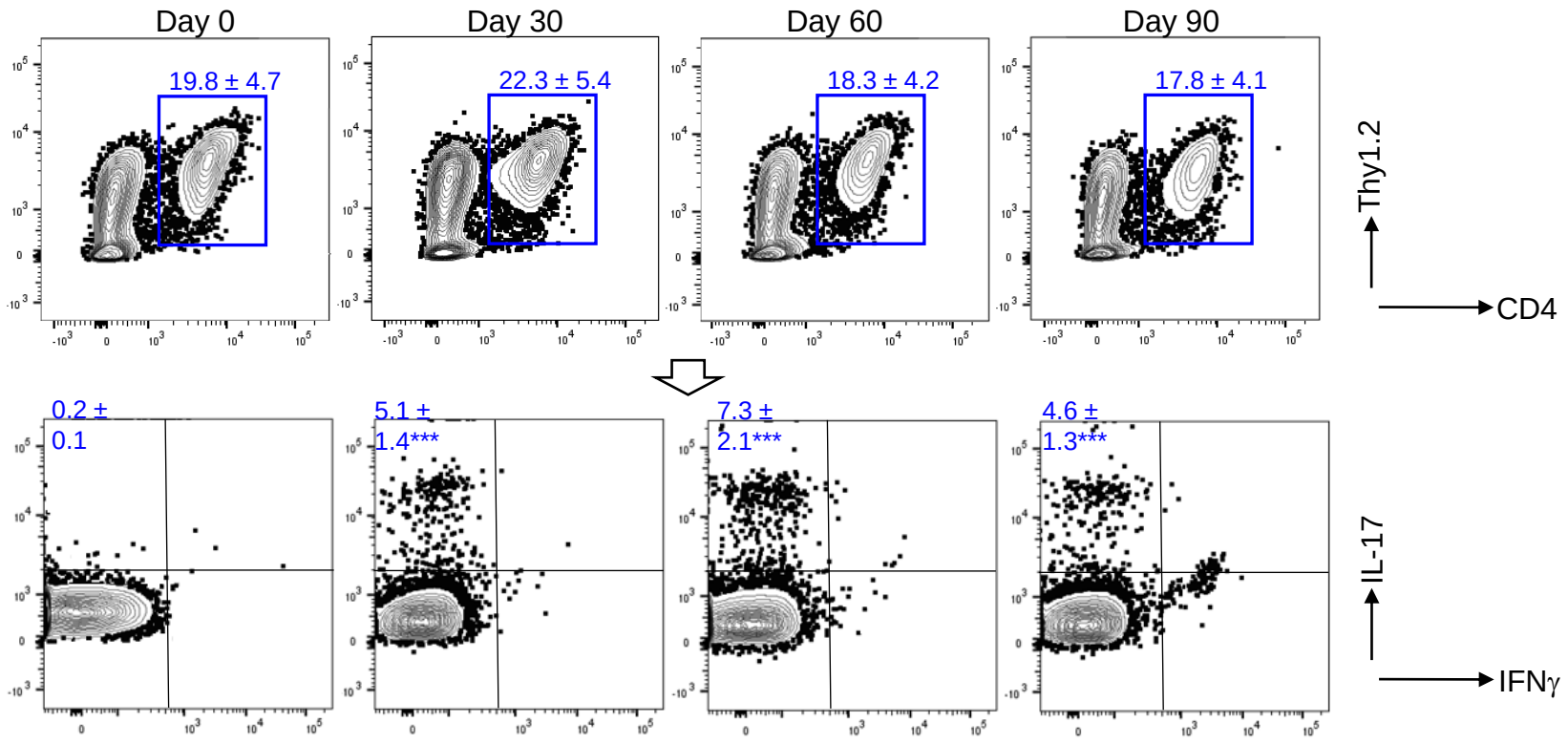
Eight-week-old C57BL/6J mice were i.v. injected with IL-23 or GFP MC for 90 days.

a. Flow cytometry quantitation of splenic Ly6G$^+$ neutrophils (Top) or IL-17 and IFNγ production from CD4 T cells (Bottom).
b. Representative Hematoxylin and Eosin stain (H&E) images of kidneys from indicated mice.
c. Flow cytometry quantitation of infiltrating CD4 T cells and Ly6G$^+$ neutrophils in kidneys.



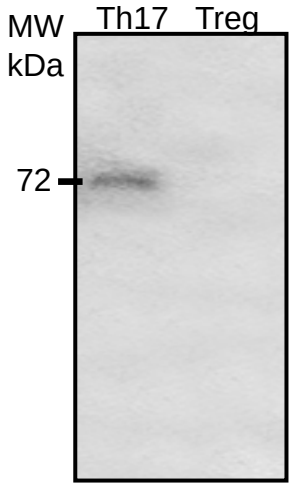
Supplemental Figure 5. IL-23 overexpression *in vivo* drives renal infiltration of CD4 T cells and Gr1$^+$ macrophages/neutrophils.

Eight-week-old C57BL/6J mice were injected with IL-23 MC for the indicated days. Bar graphs show cell counts of infiltrating CD4 T cells (Left) and Gr1$^+$ macrophages/neutrophils (Right) in kidneys. ***P < 0.005, 2-way ANOVA test;



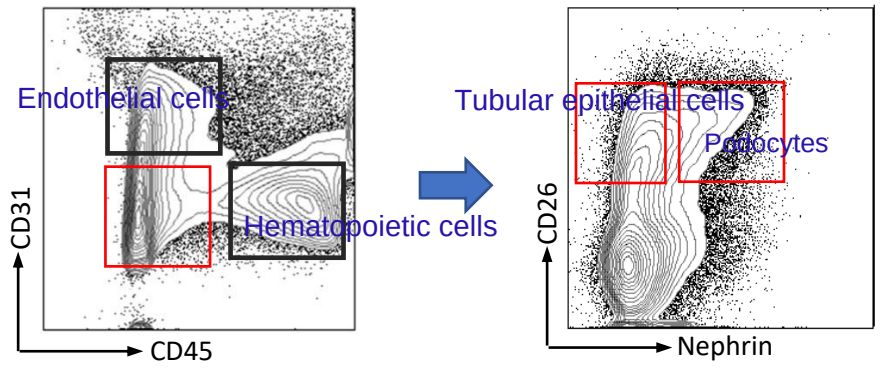
Supplemental Figure 6. IL-23 overexpression drives the expansion of splenic Th17s in vivo .

Eight-week-old C57BL/6J mice were injected with IL-23 MC for the indicated days. Flow cytometry quantitation of IL-17 and IFNγ production from CD4 T cells in the spleens.
Data represent the mean ± SEM (***P < 0.005 vs. control, Student's t test). n = 5-7 mice per group in each experiment for 2 independent experiments.



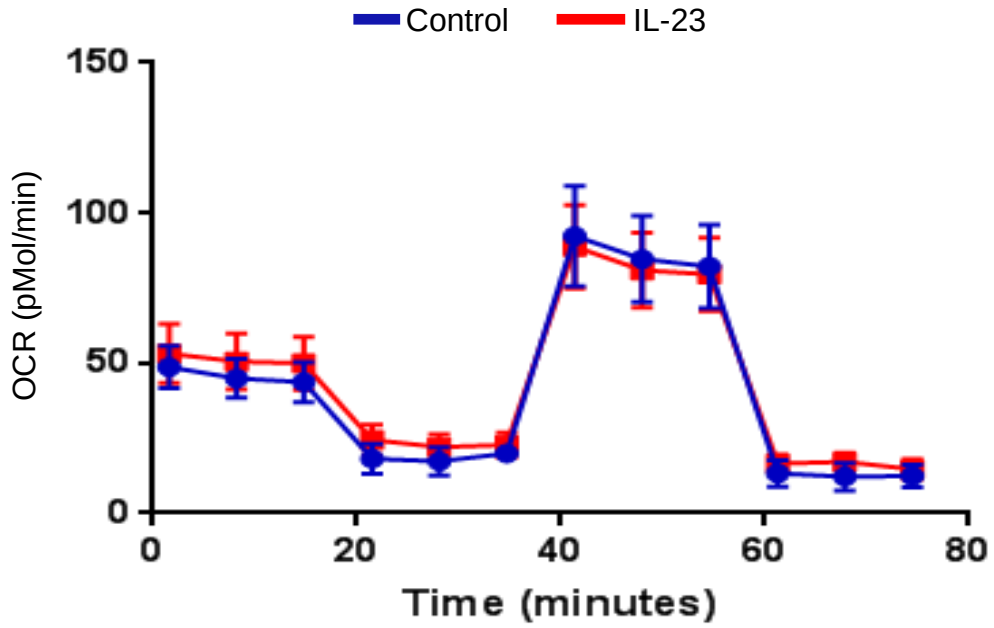
Supplemental Figure 7. IL-23R expression in polarized Th17s not Tregs by western blotting.

T cells were obtained from spleens of 12-week-old B6 mice and cultured in RPMI 1640 (Invitrogen) supplemented with 10% fetal calf serum, 2 mM glutamine, 100 IU/mL penicillin, 0.1 mg/mL streptomycin, 0.25 µg/mL amphotericin B, and 2 µM βmercaptoethanol. Cells were activated at a concentration of 106 cells/mL media in 96-well cell culture plates (Nalge Nunc) with plate-bound anti-CD3 (5 µg/mL), anti-CD28 (5 µg/mL). Treg cultures were supplemented with10 ng/mL IL-2 (R&D System), 5 ng/mL TGF-β1 (R&D Systems), 10 µg/mL anti–IL-4 (BD PharMingen), 10 µg/mL anti–IFN-γ (BD PharMingen), 10 µg/mL anti–IL-17(BD PharMingen) and Th17 conditions contained 10 ng/mL IL-6 (Invitrogen, Grand Island, NY), 5 ng/mL IL-23 (R&D Systems), 5 ng/mL TGF-β1 (R&D Systems), 10 µg/mL anti–IL-4, and 10 µg/mL anti–IFN-γ(BD PharMingen). Polarized cells were analyzed by western blotting using a goat anti-mouse/human polyclonal anti-IL-23R antibody (Abcam) followed by HRP conjugated donkey anti-goat IgG antibody (R&D Systems).



Supplemental Figure 8. Isolation of tubular epithelial cells.

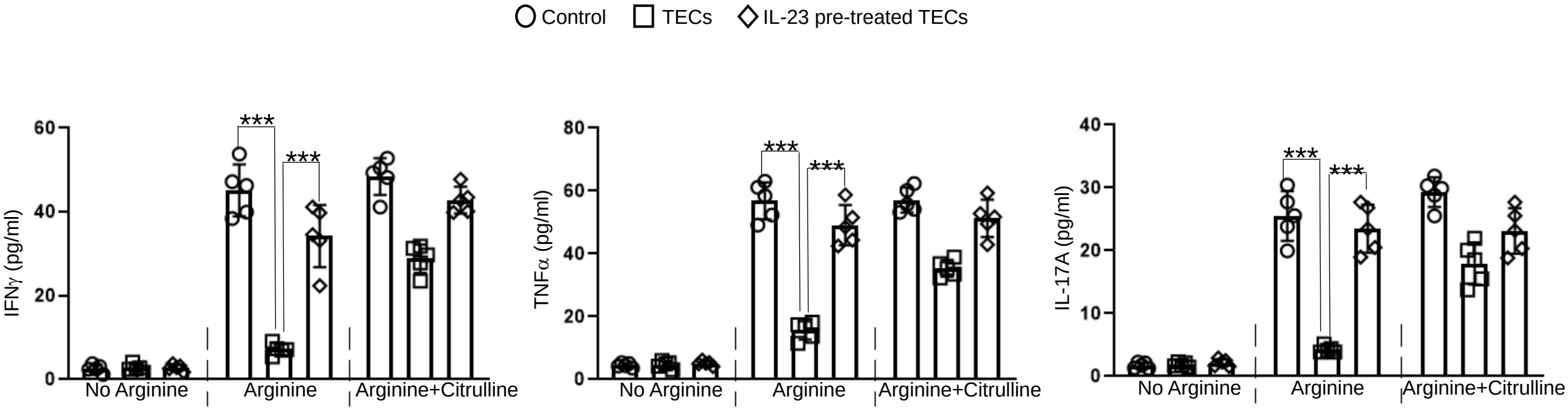
Kidney from indicated mice were collected and digested for single cell suspension by 0.5% collagenase D. Endothelial cells ($CD31^+CD45^-$) and all hematopoietic cells ($CD45^+CD31^-$) were first excluded. The remaining $CD45^-$ cells were further sorted into tubular epithelial cells or podocytes based on the expression of CD26 and nephrin (tubular epithelial cells are $CD26^+Nephrin^-$ and podocytes are $CD26^+Nephrin^+$).



Mouse primary TECs

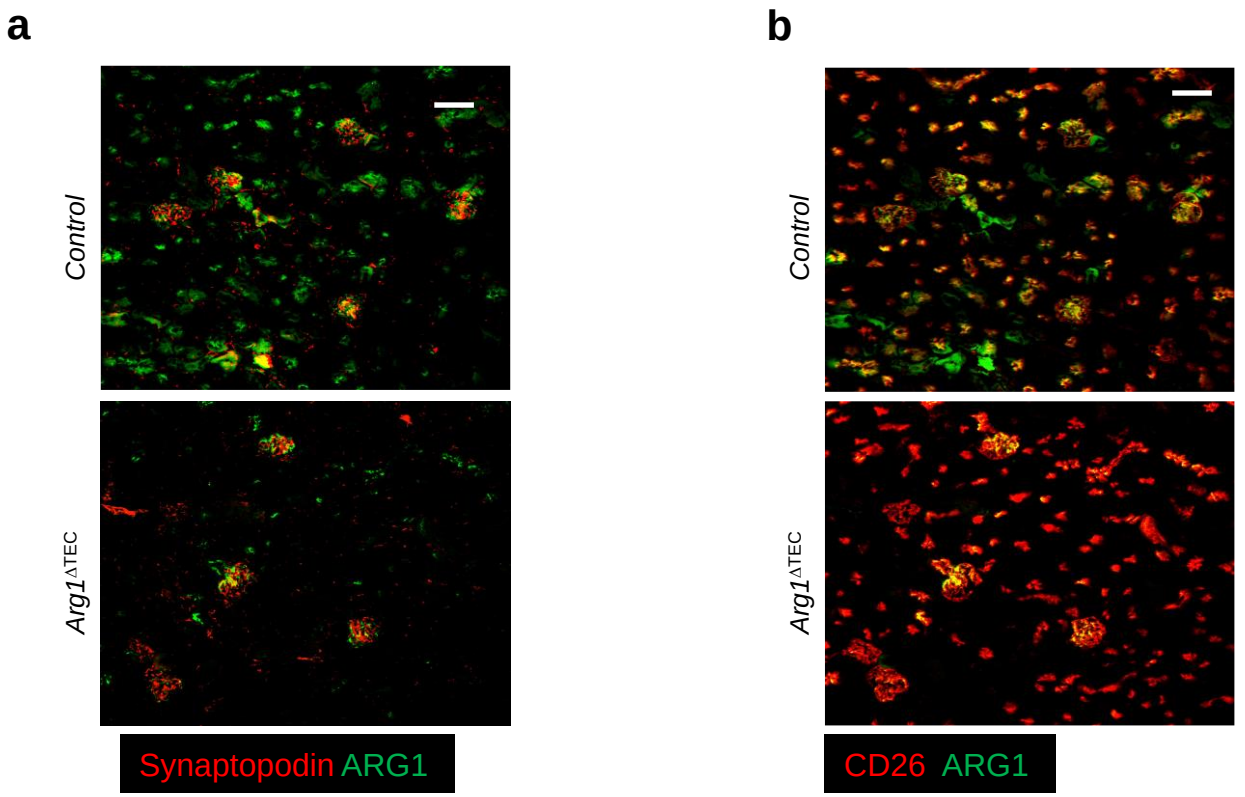
Supplemental Figure 9. IL-23 stimulation has no effect on oxygen consumption rate (OCAR) of mouse tubular epithelial cells.

Mean OCAR of *in vitro* cultured mouse primary proximal tubular epithelial cells pre-stimulated with IL-23 for 6 hrs (Red) and cells without stimulation was used as control. *n* = 3 per group in each experiment for 2 independent experiments.



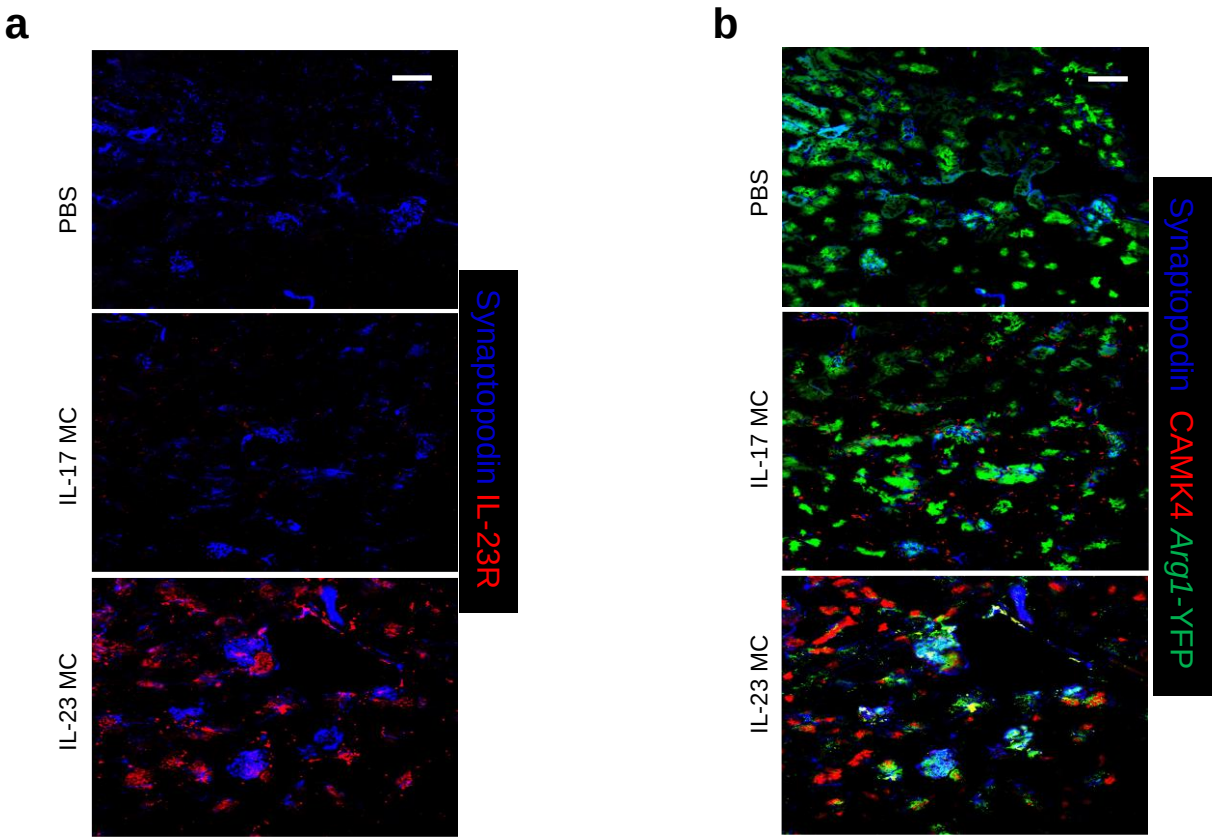
Supplemental Figure 10. Tubular epithelial IL-23 signaling enables inflammatory cytokine production from activated T cells.

Tubular epithelial cells (TEC) or TEC pre-stimulated with IL-23 for 6hrs were co-cultured with purified splenic CD4 T cells in the presence of anti-CD3 plus anti-CD28 stimulation in Arginine-deficient media. Arginine or Citrulline was added in different groups for comparison. Culture medium were collected 72 hrs after co-culture for ELISA analysis. Bar graphs show indicated cytokine concentrations. ***P < 0.005, 2-way ANOVA test;



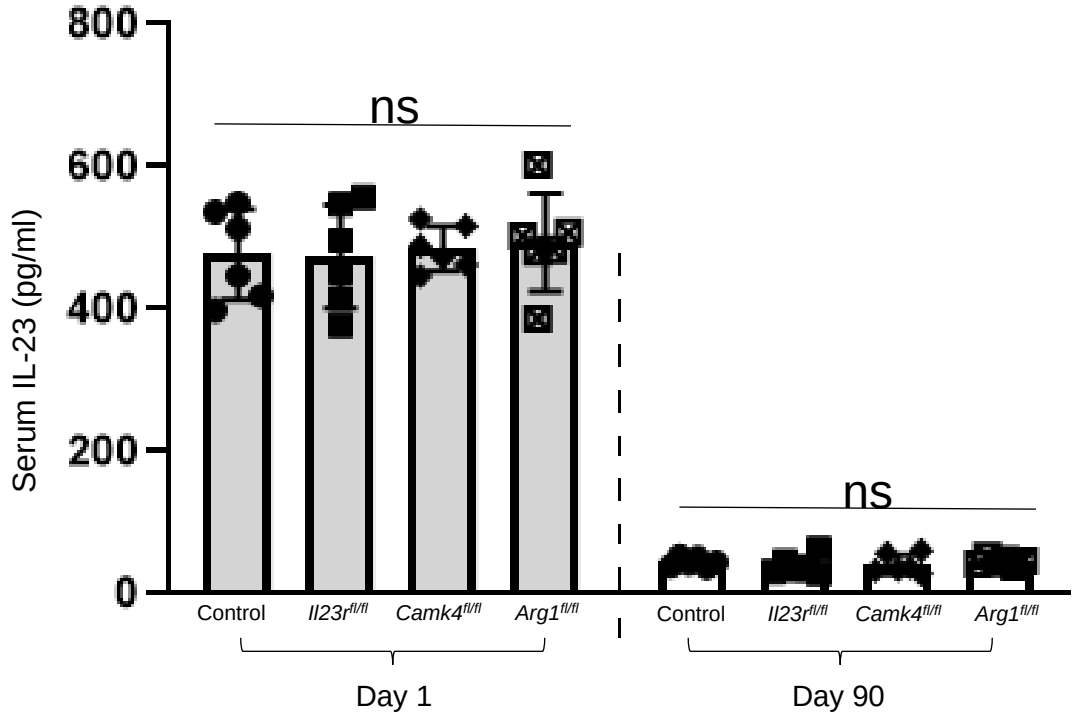
Supplemental Figure 11. *Cdh16* driven *Arg1* deletion abolish the ARG1 expression in renal interstitium but not glomeruli.

Representative confocal microscopic images of (**a**) Synaptopodin (red) and ARG1 (green) or (**b**) CD26 (red) and ARG1 (green) for representative kidneys from indicated mice. Original magnification ×5, scale bar: 150 mm.



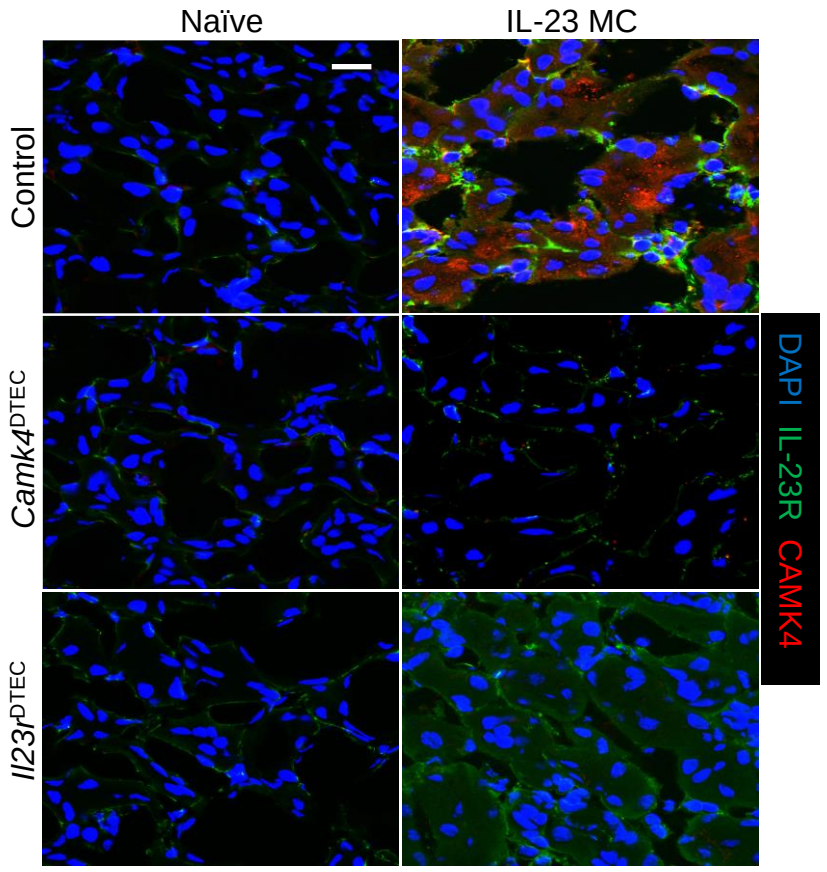
Supplemental Figure 12. IL-23 inhibits the ARG1 expression in renal interstitium but not glomeruli.

Representative confocal microscopic images of renal YFP (ARG1) for mice subjected to indicated MC administration. Original magnification ×5, scale bar: 150 mm.



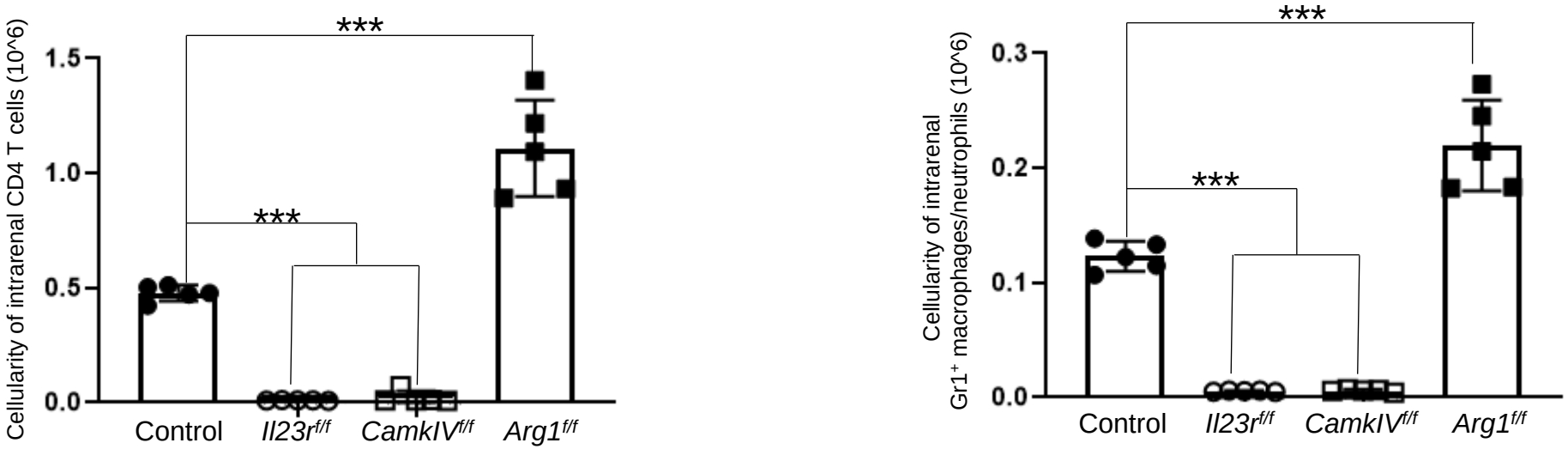
Supplemental Figure 13. Elevated expression of IL-23 in the sera of mice subjected to minicircle administration.

Eight-week-old indicated mice were i.v. injected with IL-23 and ELISA analysis of serum titers of IL-23.
n = 5-7 mice per group in each experiment for 2 independent experiments.



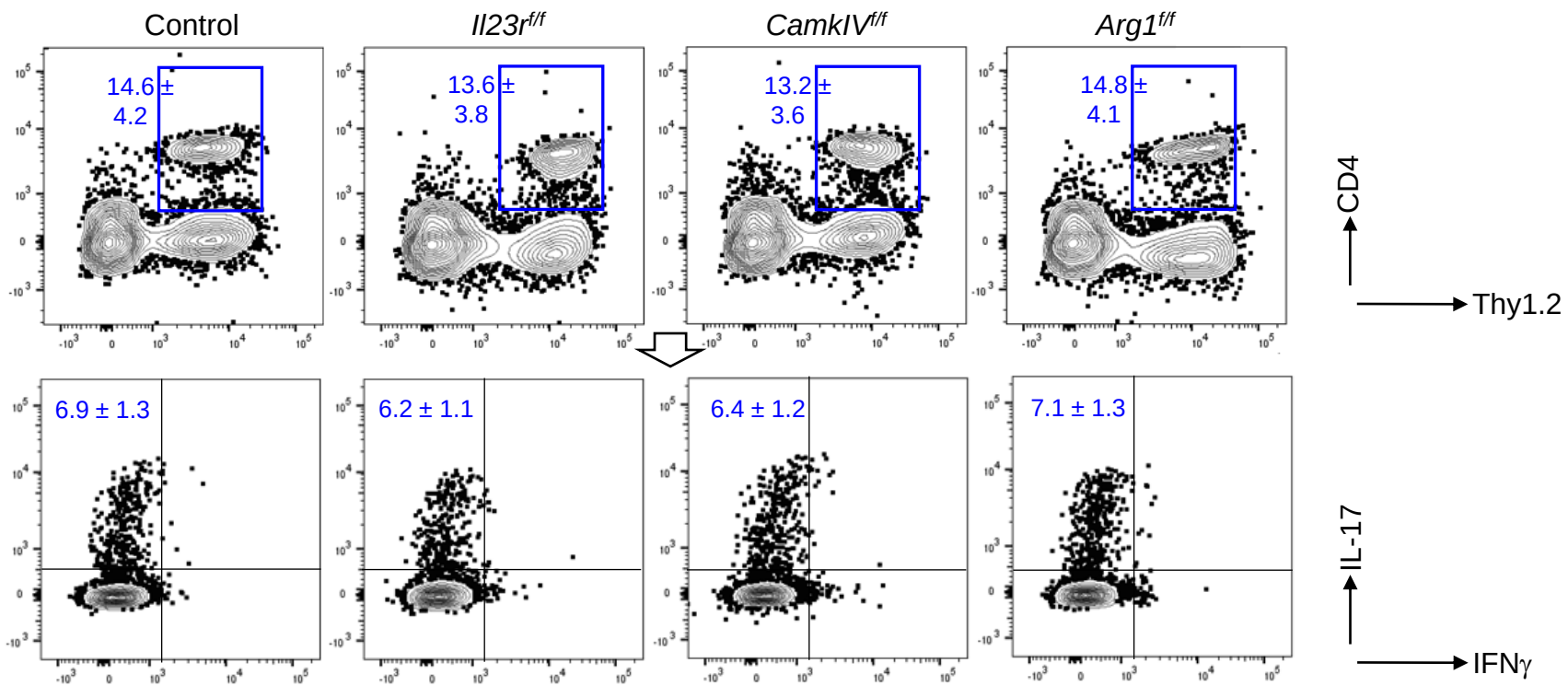
Supplemental Figure 14. IL-23 mediated induction of IL-23R and CaMK4 on Tubular epithelial cells from wild type control mice but not mice with *Cdh16* driven deficiency.

Representative confocal microscopic images of IL-23 mediated induction of IL-23R (green) and CaMK4 (red) on TECs in renal interstitium for mice subjected to indicated MC administration. Magnification, ×20. Scale bar: 20 mm.



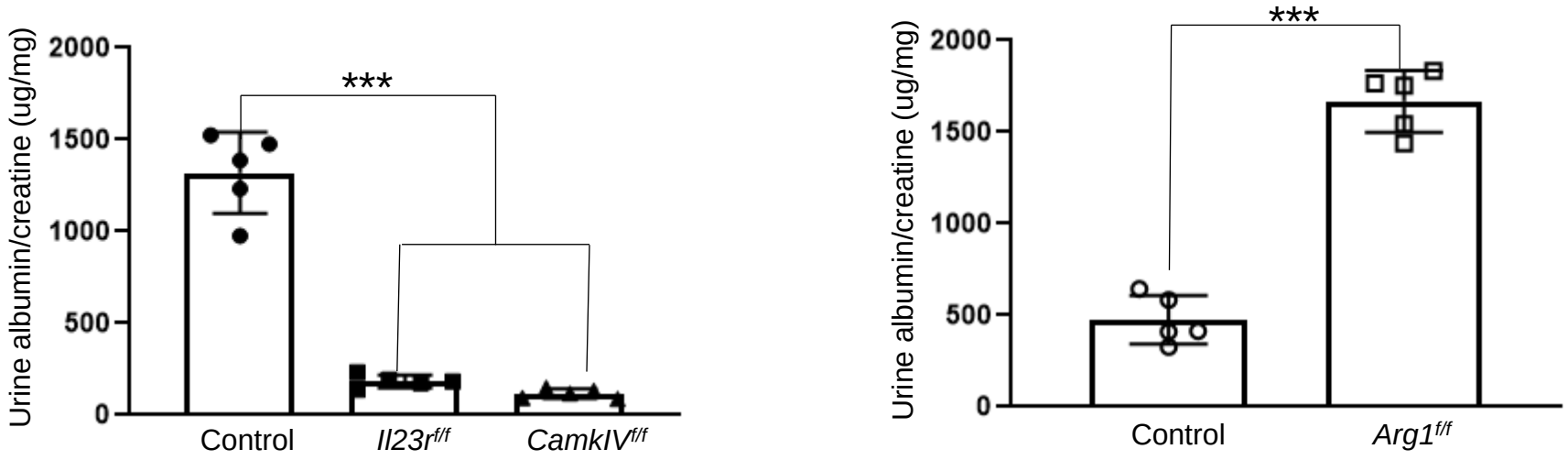
Supplemental Figure 15. Genetic deficiency of *Il23r* or *Camk4* ameliorates but deficiency of *Arg1* exaggerates IL-23 mediated renal inflammation.

Eight-week-old mice with indicated genotypes were injected with IL-23 MC for 90 days. All mice are *Cdh16*-cre^{+}. Bar graphs show the cell counts of renal infiltrating CD4 T cells (Left) and Gr1^{+} macrophages/neutrophils (Right). ***P < 0.005, 2-way ANOVA test;



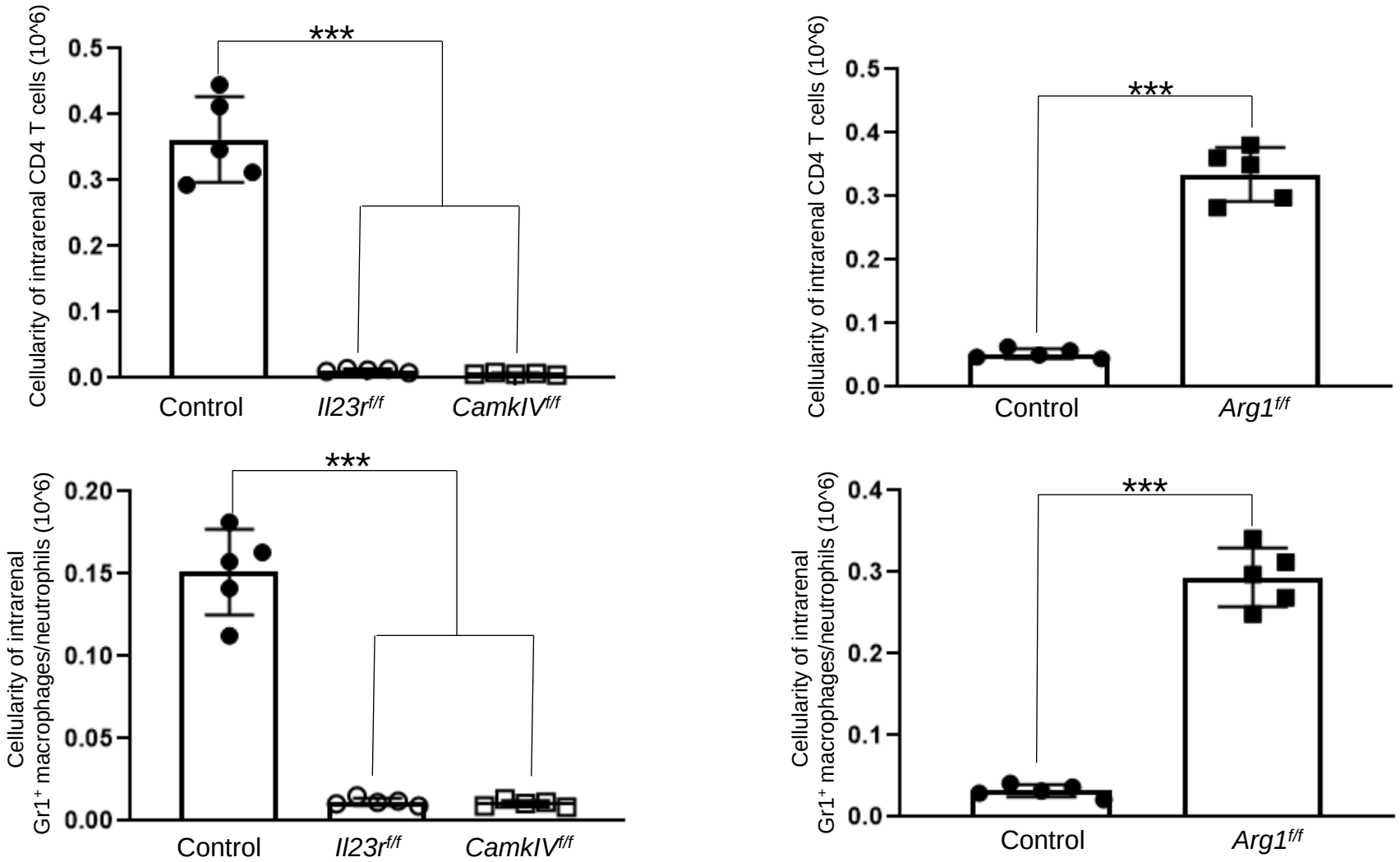
Supplemental Figure 16. Genetic deficiency of *Il23r, Camk4* and *Arg1* do not affect the accumulation of splenic Th17s driven by administered IL-23 MC.

Eight-week-old mice with indicated genotypes were injected with IL-23 MC for 90 days. All mice are *Cdh16*-cre^{+}. Flow cytometry quantitation of IL-17 and IFNγ production from CD4 T cells in the spleens.
Data represent the mean ± SEM. *n* = 5-7 mice per group in each experiment for 2 independent experiments.



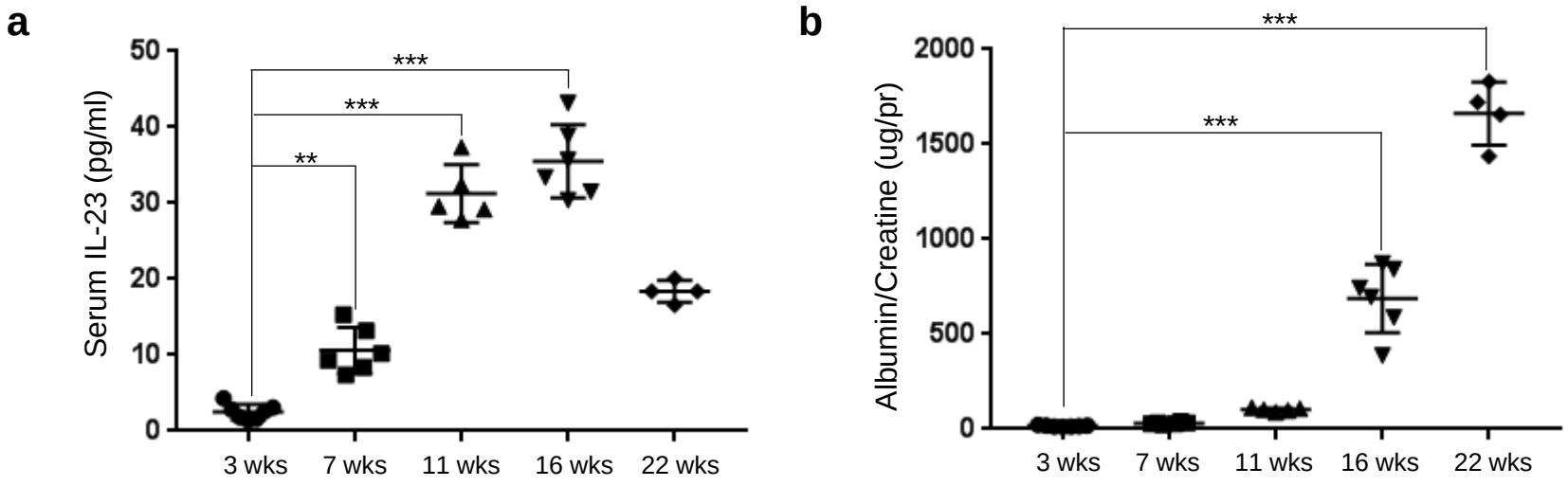
Supplemental Figure 17. Genetic deficiency of *Il23r, Camk4* or *Arg1* ameliorates but deficiency of *Arg1* exaggerates proteinuria in anti-GBM murine model.

100 ul (Left) or 50 ul (Right) sheep anti-mouse glomerular basement membrane *(*GBM*)* serum was administered to 8-week-old mice with indicated genotypes for 21 days to induce immune-mediated glomerulonephritis. All mice are *Cdh16*-cre^{+}. ELISA quantitation of protein in urine from mice subjected to the indicated treatment and bar graphs show the mean ratio of urine albumin and creatinine from mice subjected to the indicated treatment.



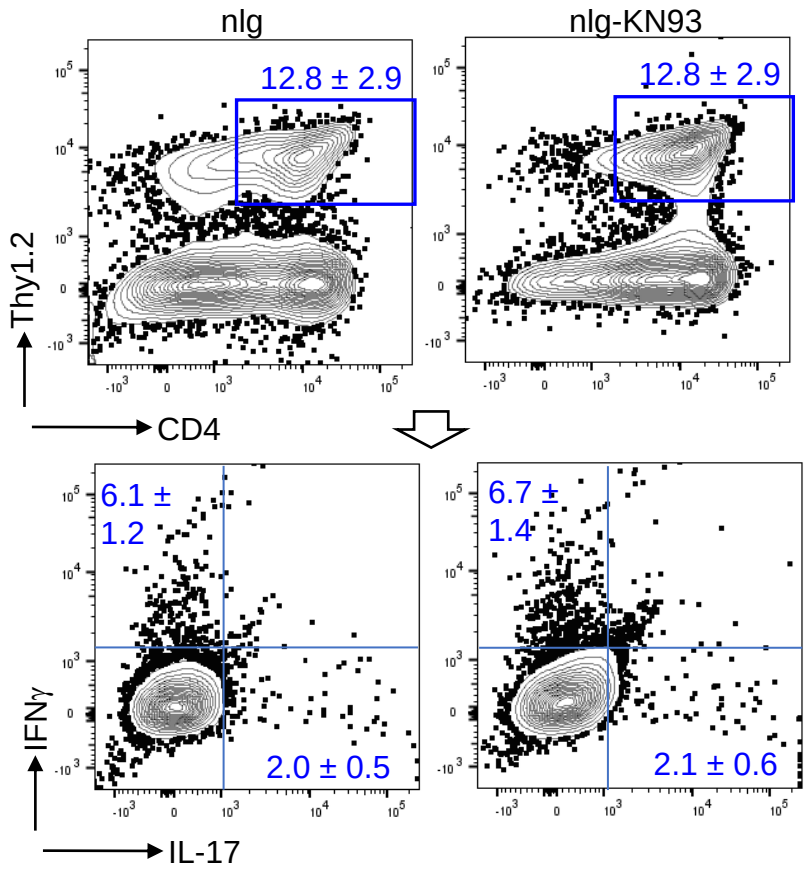
Supplemental Figure 18. Genetic deficiency of *Il23r* or *Camk4* ameliorates but deficiency of *Arg1* exaggerates toxic GBM serum mediated renal inflammation.

100 ul (Left) or 50 ul (Right) sheep anti-mouse glomerular basement membrane *(*GBM*)* serum was administered to 8-week-old mice with indicated genotype for 21 days for the induction of immune-mediated glomerulonephritis. All mice are *Cdh16*-cre^{+}. Bar graphs show the cell counts of renal infiltrating CD4 T cells (Top) and Gr1^{+} macrophages/neutrophils (Bottom).
***P < 0.005, *t* tests (2-tailed) for 2 groups, 2-way ANOVA with Bonferroni's multiple comparisons tests for 3 groups.



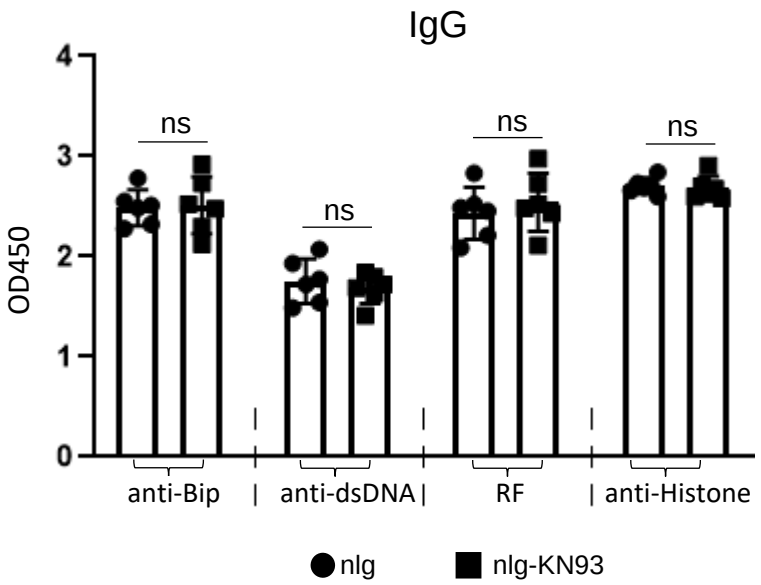
Supplemental Figure 19. Elevation of IL-23 in the sera precedes the appearance of proteinuria in lupus prone MRL/lpr mice.

(a) ELISA analysis of IL-23 in the sera from MRL/lpr mice with indicated ages. (b) The ratio of urine albumin to creatinine from MRL/lpr mice with indicated ages. Data represent the mean ± SEM. n = 6 mice per group in each experiment for 2 independent experiments. *P < 0.05, ***P < 0.005, 2-way ANOVA tests.



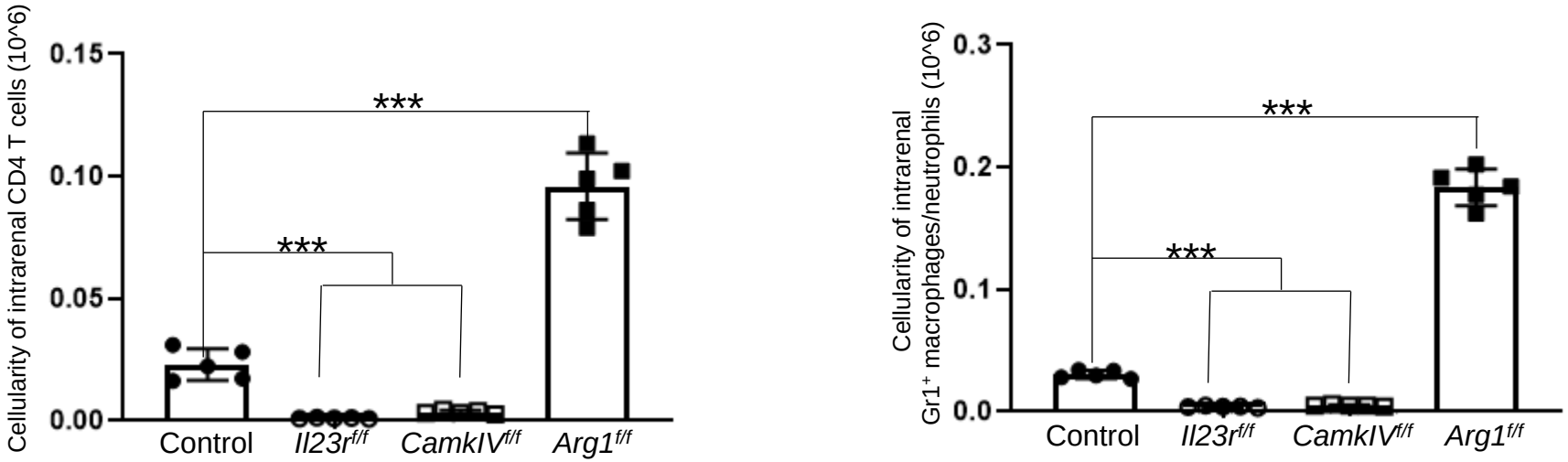
Supplemental Figure 20. TEC-targeted delivery of KN93, a CaMK4 inhibitor does not affect splenic CD4 T cell activation.

Female MRL/lpr mice were treated with anti-CDH16 antibody coated-nanolipogel-KN93 weekly starting at 10 weeks of age and euthanized at 16 weeks of age for analysis. Flow cytometry quantitation of IL-17 and IFNγ production from CD4 T cells in the spleens. Data represent the mean ± SEM. *n* = 4-5 mice per group in each experiment for 2 independent experiments.



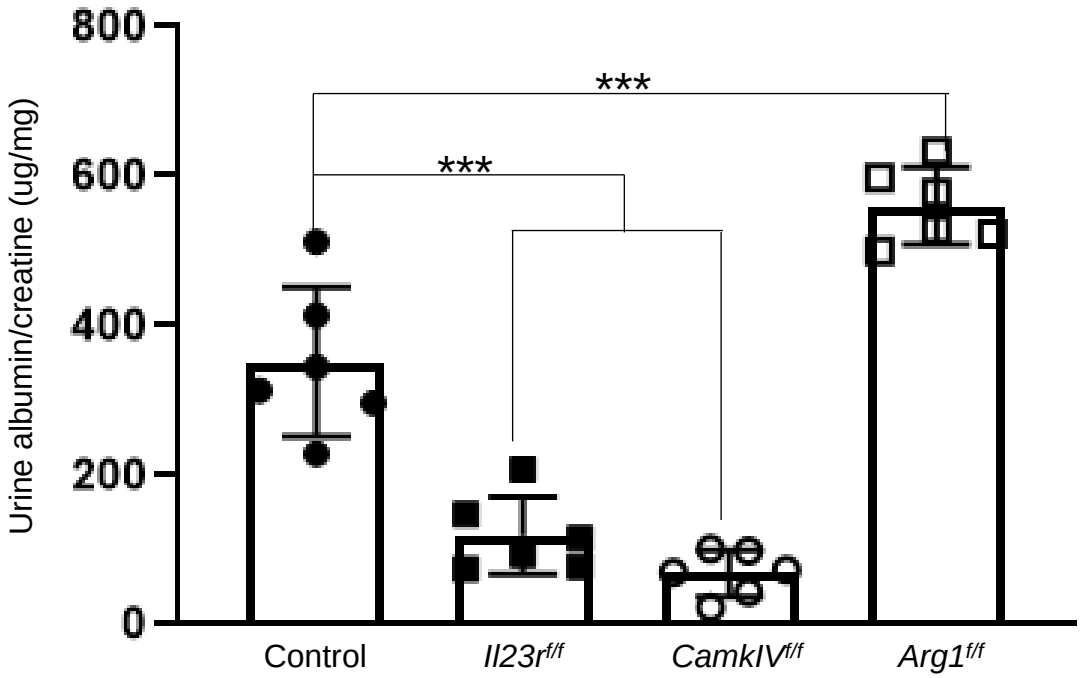
Supplemental Figure 21. TEC-targeted delivery of KN93, a CaMK4 inhibitor has no effects on circulating autoantibody production.

Female MRL/lpr mice were treated with anti-CDH16 antibody coated-nanolipogel-KN93 weekly starting at 10 weeks of age and euthanized at 16 weeks of age for analysis. ELISA quantification of circulating autoantibodies in the serum.



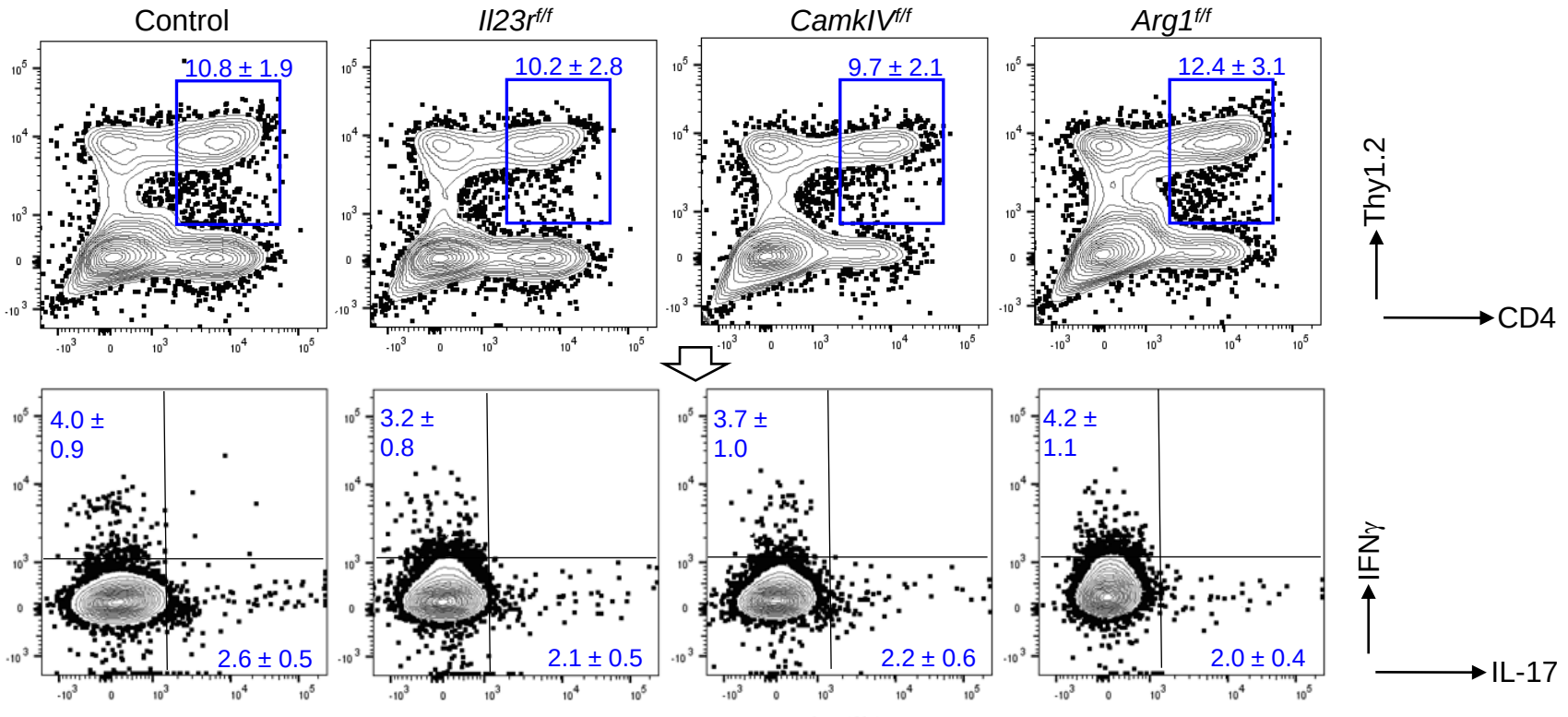
Supplemental Figure 22. Genetic deficiency of *Il23r, Camk4 or Arg1* ameliorates but deficiency of *Arg1* exaggerates renal inflammation in lupus murine model.

Bone marrow (BM) reconstitution was carried out by transferring BM from 2 months old wild type B6.*lpr* to lethal irradiated B6 recipients with indicated genotypes. Recipient mice were euthanized 10 months after BM reconstitution. All mice are *Cdh16*-cre^{+}. Bar graphs show the cell counts of renal infiltrating CD4 T cells (Left) and Gr1^{+} macrophages/neutrophils (Right). ***P < 0.005, 2-way ANOVA tests.



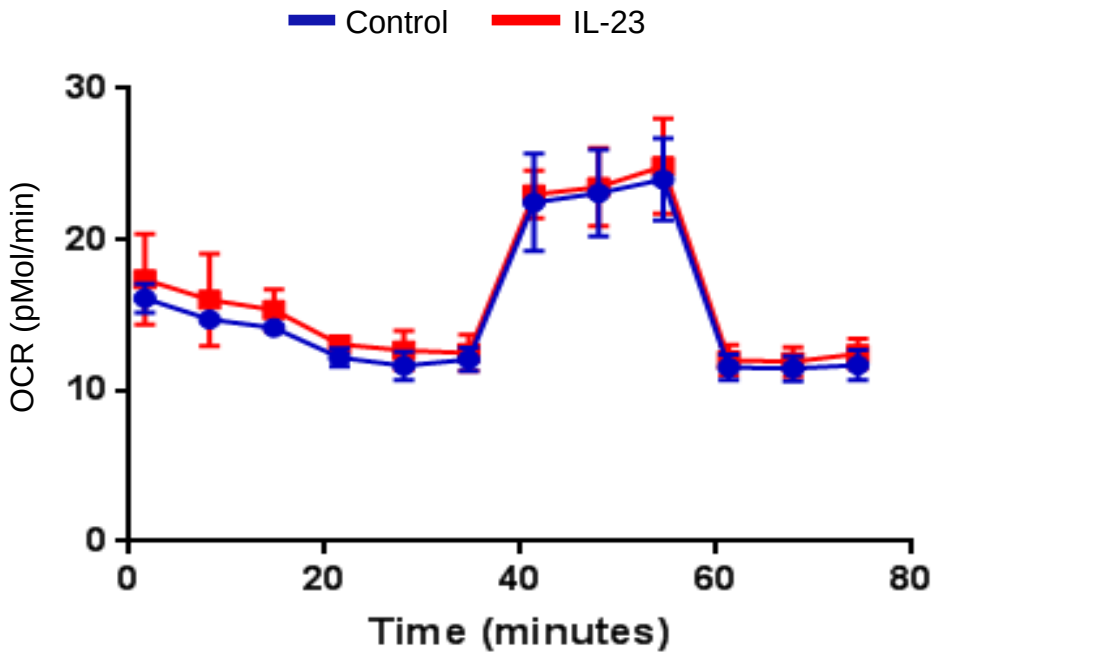
Supplemental Figure 23. Genetic deficiency of *Il23r, Camk4 or Arg1* ameliorates but deficiency of *Arg1* exaggerates proteinuria in lupus murine model.

Bone marrow (BM) reconstitution was carried out by transferring BM from 2 months old wild type B6.*lpr* to lethal irradiated B6 recipients with indicated genotypes. Recipient mice were euthanized 10 months after BM reconstitution. All recipients are *Cdh16*-cre^{+}. ELISA quantitation of protein in urine from mice subjected to the indicated treatment and bar graphs show the mean ratio of urine albumin and creatinine from mice subjected to the indicated treatment. ***P < 0.005, 2-way ANOVA tests.



Supplemental Figure 24. Genetic deficiency of *Il23r, Camk4 or Arg1* does not affect splenic T cell activation.

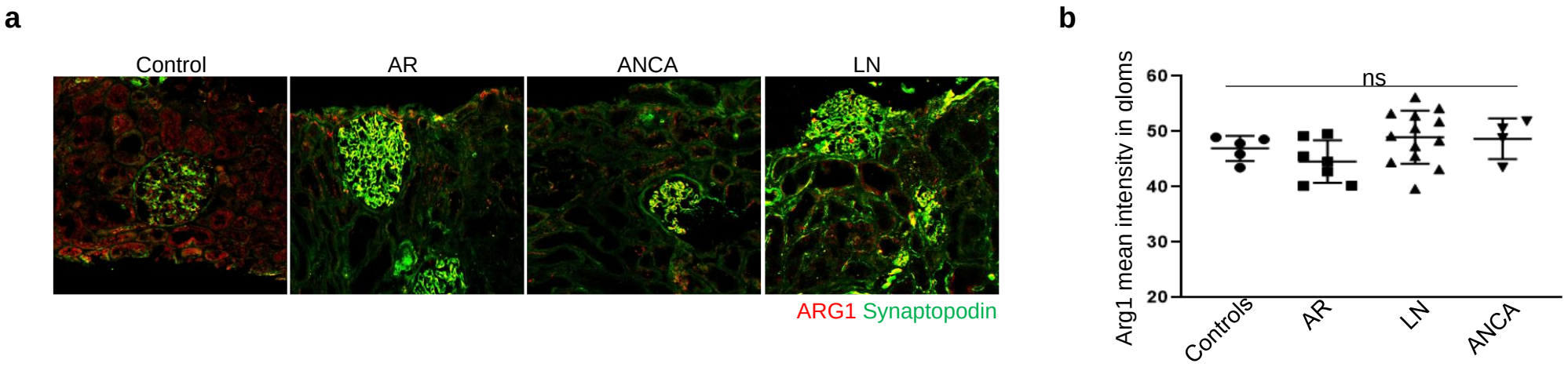
Bone marrow (BM) reconstitution was carried out by transferring BM from 2 months old wild type B6.*lpr* to lethal irradiated B6 recipients with indicated genotypes. Recipient mice were euthanized 10 months after BM reconstitution. All recipients are *Cdh16*-cre^{+}. Flow cytometry quantitation of IL-17 and IFNγ production from CD4 T cells in the spleens.
Data represent the mean ± SEM. *n* = 4-6 mice per group in each experiment for 2 independent experiments.



Human primary TECs

Supplemental Figure 25. IL-23 stimulation has no effect on oxygen consumption rate (OCAR) of human tubular epithelial cells.

Mean OCAR of *in vitro* cultured human primary proximal tubular epithelial cells pre-stimulated with IL-23 for 6 hrs (Red) and cells without stimulation was used as control. *n* = 3 per group in each experiment for 2 independent experiments.



Supplemental Figure 26. ARG1 expression was not downregulated in glomeruli in renal biopsies from patients with glomerulonephritis.

Cryosection of human kidney biopsies from indicated group. Representative fluorescence photomicrographs (a) and ImageJ 3D intensity plots (b) for ARG1. Magnification, ×20. Scale bar: 50 mm. Control: Healthy donor; AR: Allograft rejection; ANCA: ANCA Glomerulonephritis; LN: lupus nephritis.

Patient No.	Diseases	Activity index	Chronicity index	Intersitial fibrosis (IF) and tubular atrophy (TA)	IL-23R expression on TEC	CAMK4 expression on TEC
1	Class III Lupus Nephritis (LN)	4/24	1/12	<5% IF and TA	++	++
2	Class III LN	11/24	1/12	<10% IF and TA	++	++
3	Class III LN	3/24	0/12	<5% IF and TA	++	++
4	Class III LN (endocapillary proliferative glomerulonephritis)	3/24	1/12	10% IF and TA	+++	++
5	LN Class III and V	1/24	0/12	10%-15% IF and TA	++	++
6	Class IV-G diffuse LN (A+C) and class V	5/24	4/12	15% IF and TA	+++	++
7	Class IV (A+C) and Class V	6/24	9/12	60% IF and TA	+++	+++
8	Class IV (A+C)	4/24	8/12	35% IF and TA	+++	+++
9	Active Class IV	20/24	Not available	<25% IF and TA	++	++
10	Class IV (A+C)	4/24	8/12	25%-50% IF and TA	+++	+++
11	Class IV (A+C) and Class V	6/24	9/12	>50% IF and TA	+++	+++
12	Class IV-G diffuse (A+C) and Class V	16/24	4/12	25% IF and TA	+++	+++
13	Class IV-G diffuse LN (A+C) and class V.	5/24	4/12	25% IF and TA	+++	+++
14	Class III LN after treatment, no active disease and no deposits	0	0	0	Dim or negative expression	Negative
15	Class IV and Class V LN after treatment. NO proliferative component.	0	0	0	negative	Negative
16	Class IV and Class V LN after treatment. NO proliferative component.	0	0	<5% IF and TA	Dim or negative expression	Dim or negative expression
17	Class VI. No active disease. No deposits	0	0	50% IF and TA	Dim or negative expression	Dim

Supplemental Table 1. Clinical and histological characteristics of subjects with lupus nephritis at the time of renal biopsy (n=17).
IL-23R expression was scored as follows: ++: 30%–50%; +++: >50%;

Patient No.	Diseases	Intersitial fibrosis and tubular atrophy	IL-23R expression on TEC	CAMK4 expression on TEC
1	ANCA associated glomerulonephritis	None	+++	+++
2	ANCA associated glomerulonephritis	None	+++	+++
3	ANCA associated glomerulonephritis	10% IF and TA	+++	+++
4	ANCA associated glomerulonephritis	60% IF and TA	+++	+++

Supplemental Table 2. Clinical and histological characteristics of subjects with ANCA associated glomerulonephritis at the time of renal biopsy (n=4).

IL-23R expression was scored as follows: +++: >50%;

Patient No.	Diseases	Duration (Months)	Banff scoring IFTA	Banff Lesion Score ti (Total Inflammation)	IL-23R expression on TEC	CAMK4 expression on TEC
1	Allograft with possible cellular rejection	45	1+1	1	++	+
2	Allograft with cellular rejection	72	2+2	2	++	+++
3	Allograft with acute cellular rejection	3.5	0	3	+	+
4	Allograft with acute Cellular Rejection	0.5	1+1	3	+	+
5	Allograft with cellular rejection with Tubulitis	60	3+3	3	++	++
6	Allograft with cellular rejection	Not available	1+1	2	+	+
7	Allograft with acute Cellular Rejection with IgA nephropathy	Not available	1+1	3	++	++

Supplemental Table 3. Clinical and histological characteristics of subjects with Renal Transplantation Rejection at the time of renal biopsy (n=7).

IL-23R expression was scored as follows: +: 10%–30%; ++: 30%–50%; +++: >50%;