

Mineralocorticoid Receptor Deficiency in T Cells Attenuates Pressure Overload–Induced Cardiac Hypertrophy and Dysfunction Through Modulating T-Cell Activation

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Abstract—Although antagonists of mineralocorticoid receptor (MR) have been widely used to treat heart failure, the underlying mechanisms are incompletely understood. Recent reports show that T cells play important roles in pathologic cardiac hypertrophy and heart failure. However, it is unclear whether and how MR functions in T cells under these pathologic conditions. We found that MR antagonist suppressed abdominal aortic constriction–induced cardiac hypertrophy and decreased the accumulation and activation of CD4⁺ and CD8⁺ T cells in mouse heart. T-cell MR knockout mice manifested suppressed cardiac hypertrophy, fibrosis, and dysfunction compared with littermate control mice after abdominal aortic constriction. T-cell MR knockout mice had less cardiac inflammatory response, which was illustrated by decreased accumulation of myeloid cells and reduced expression of inflammatory cytokines. Less amounts and activation of T cells were observed in the heart of T-cell MR knockout mice after abdominal aortic constriction. In vitro studies showed that both MR antagonism and deficiency repressed activation of T cells, whereas MR overexpression elevated activation of T cells. These results demonstrated that MR blockade in T cells protected against abdominal aortic constriction–induced cardiac hypertrophy and dysfunction. Mechanistically, MR directly regulated T-cell activation and modulated cardiac inflammation. Targeting MR in T cells specifically may be a feasible strategy for more effective treatment of pathologic cardiac hypertrophy and heart failure. (*Hypertension*. 2017;70:137–147. DOI: 10.1161/HYPERTENSIONAHA.117.09070.) • [Online Data Supplement](#)

Key Words: cardiac hypertrophy ■ heart failure ■ mineralocorticoid receptor ■ T cells ■ T-cell activation

Pathologic cardiac hypertrophy is a maladaptation of the heart responding to conditions such as chronic hypertension and myocardial infarction.¹ The pathologic remodeling of the heart is often associated with deleterious disorders, including cardiac fibrosis, chronic inflammatory response, and cardiac dysfunction, leading to heart failure, which remains to be a leading cause of mortality and morbidity around the world.² Better understanding of the underlying pathophysiology and development of novel strategies are in need to achieve better outcome in treating pathologic cardiac hypertrophy and heart failure.

T cells have emerged as an important cellular compartment for targeting pathologic cardiac hypertrophy and heart failure.^{3,4} In particular, recent data have revealed that activation of T cells plays a fundamental role in pressure overload

(POL)–induced cardiac hypertrophy and heart failure. Deletion of T-cell receptor alpha, an important component of signal 1 of T-cell activation, reduces cardiac fibrosis, hypertrophy, and inflammation, as well as improves cardiac function and survival in a mouse model of POL.⁵ Similarly, deletion or blockade of CD28 or B7, essential components of signal 2 of T-cell activation, attenuates POL-induced cardiac hypertrophy, heart failure, cardiac inflammation, and T-cell accumulation.⁶ Interestingly, CD4⁺ T cells, but not CD8⁺ T cells, are critical in the transition from cardiac hypertrophy to heart failure in response to POL.⁷ Therefore, it may be a feasible strategy to identify key molecules that regulate T-cell function and that ultimately intervene in cardiac hypertrophy and heart failure.

Mineralocorticoid receptor (MR) is an important drug target for treating heart failure. Clinical trials have

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convincingly demonstrated the beneficial effects of MR antagonists for heart failure patients.^{8–10} Similar results were observed in murine models of cardiac hypertrophy and heart failure.^{11,12} However, the usage of MR antagonists, spironolactone and eplerenone, remains suboptimal at least partially because of their side effects.¹³ Delineating the underlying mechanisms may facilitate better usage of spironolactone and eplerenone and help to develop new generation of MR antagonists.

Studies in recent years have shed some light on the cellular and molecular mechanisms of how MR functions in the setting of cardiac hypertrophy and heart failure, although they remain to be incompletely understood. Cardiomyocyte MR deficiency improves cardiac dysfunction in a mouse model of myocardial infarction.¹⁴ Although MR deletion in cardiomyocyte protects end-stage heart failure induced by POL, it has no effect on cardiac hypertrophy or fibrosis in this model.¹⁵ Macrophage MR deficiency attenuates cardiac hypertrophy and remodeling in various mouse models of POL, including aortic constriction¹⁶ and treatment with NG-nitro-L-arginine methyl ester/angiotensin II¹⁷ or deoxycorticosterone/salt.^{18,19} Mechanistically, MR in macrophages has been demonstrated to control macrophage polarization.¹⁷ However, the function of T-cell MR in pathologic cardiac hypertrophy and heart failure has not been explored.

In this study, we set out to determine whether and how MR in T cells affects pathologic cardiac hypertrophy and dysfunction. We first study the impacts of eplerenone on pathologic cardiac hypertrophy and T-cell activation. Then, we used T-cell MR knockout (TMRKO) mouse model to further establish the roles of T-cell MR in cardiac hypertrophy, fibrosis, dysfunction, and cardiac inflammation. Subsequently, we determine the effects of TMRKO on T-cell accumulation and activation in the heart. Finally, we explore the direct influence of MR on T-cell activation in vitro.

Methods

Animals and Surgeries

TMRKO mice were generated by crossing floxed MR mice with CD4-Cre mice as previously described.²⁰ Male C57BL6/J mice were purchased from SLAC Laboratory Animal Co. Eplerenone was mixed in regular rodent chow (2 g/kg; SLAC Laboratory Animal Co.) and administrated 3 days before surgeries until the end of experiments to deliver a dosage of ≈ 200 mg/kg/d. Abdominal aortic constriction (AAC) was performed according to previous report.^{16,21,22} Briefly, male mice (8–12 weeks old) were anesthetized with 2% isoflurane inhalation. Silk sutures (6–0) were used to ligate abdominal aortas against a blunted 27G needle above both renal arteries.²¹ The needle was then removed immediately. For sham operation, sutures were passed under aortas without ligation. Blood pressure was measured using radiotelemetry system as previously described with modifications.^{23,24} Pressure transmitters (PA-C10; Data Sciences International) were placed 3 days after AAC, and data were collected after recovery for another 4 days.

All mice were in C57BL6/J background and housed in a specific pathogen-free facility. Animal studies were approved by the Institutional Review and Ethics Board of Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine and the Institutional Animal Care and Use Committee of Institute for Nutritional Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences.

Statistical Analysis

The results were presented as mean \pm SE and analyzed using Prism (GraphPad Software). Multiple comparisons were tested with 2-way analysis of variance followed by Bonferroni posttests. Pairwise comparisons were analyzed by Student's *t* test. Results were considered significantly different if *P* values were ≤ 0.05 .

Detailed methods are available in the [online-only Data Supplement](#).

Results

Eplerenone Inhibits AAC-Induced Cardiac Hypertrophy and T-Cell Activation

Similar to previous reports,^{11,25} eplerenone significantly decreased ventricular weight-to-body weight ratio in mice 1 week after AAC, illustrating suppression of cardiac hypertrophy (Figure S1A in the [online-only Data Supplement](#)). We then analyzed cardiac T cells using flow cytometry (Figure S1B). AAC markedly induced accumulation of both CD4⁺ and CD8⁺ T cells in the heart, and this was substantially inhibited by eplerenone treatment (Figure 1A). In addition, activated T cells (CD69⁺) were upregulated in hypertrophic hearts, and eplerenone decreased CD69⁺ T cells in both CD4⁺ and CD8⁺ subpopulations (Figure S1C; Figure 1B and 1C).

Recent data have indicated the involvement of memory T cells in pathologic cardiac remodeling.²⁶ Moreover, effector memory T cells (T_{EM}⁺ CD44^{hi}CD62L^{low}) are the main source of inflammatory cytokines, such as IFN γ (interferon- γ).^{27,28} We further analyzed this T-cell subpopulation using flow cytometry (Figure S1D). Eplerenone significantly decreased the accumulation of both CD4⁺ and CD8⁺ T_{EM} cells in heart samples after AAC (Figure 1D and 1E). Furthermore, eplerenone suppressed both CD4⁺ IFN γ ⁺ and CD8⁺ IFN γ ⁺ T cells (Figure S1D through S1F). Eplerenone did not significantly alter blood pressure under AAC (Figure S2). These results indicated that eplerenone suppressed cardiac hypertrophy at least partially through its impacts on T cells, independently of its effects on blood pressure.

T-Cell MR Deficiency Attenuates AAC-Induced Cardiac Hypertrophy and Fibrosis

To further test whether blockade of MR in T cells specifically would affect cardiac hypertrophy, TMRKO mouse was generated.²⁰ Ventricular weight-to-body weight ratio demonstrated significantly less cardiac hypertrophy in TMRKO mice than in littermate control mice 1 and 6 weeks after AAC (Figure 2A). Hematoxylin and eosin staining of cross sections of left ventricles showed significantly decreased cardiomyocyte size in TMRKO mice after AAC (Figure 2B; Figure S3A). Picrosirius red staining showed that TMRKO effectively decreased AAC-induced cardiac fibrosis (Figure 2C; Figure S3B). Consistently, quantitative reverse transcriptase polymerase chain reaction analysis revealed that cardiac expression of fetal genes, such as *natriuretic peptide A* (ANP), *natriuretic peptide B* (BNP), and *cardiac myosin heavy chain β* (β MHC), was significantly inhibited in TMRKO mice after AAC (Figure 2D). Cardiac expression of fibrosis-related genes, such as *collagen I*, *collagen III*, *connective tissue growth factor precursor* (CTGF), and *transforming growth factor β* (TGF β 1), was also inhibited in TMRKO mice after AAC (Figure 2E). Telemetric

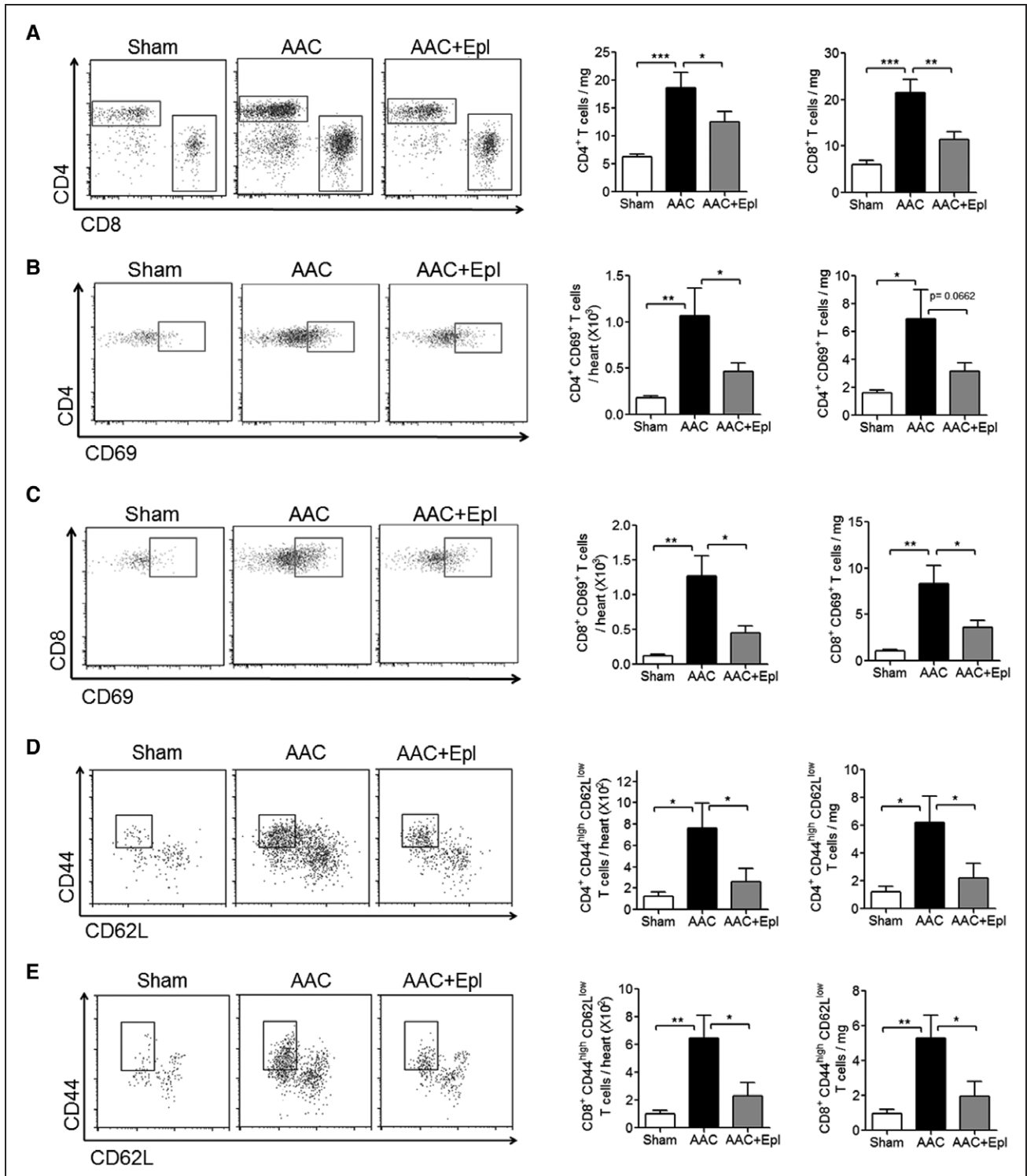


Figure 1. Mineralocorticoid receptor (MR) antagonist inhibits abdominal aortic constriction (AAC)–induced T-cell accumulation and activation in heart samples. **A**, Flow cytometric analysis of T cells in heart samples from mice undergone sham operation or AAC and fed with or without eplerenone (Epl). $n=7:8:8$. **B**, Flow cytometric analysis of CD4⁺ CD69⁺ T cells in heart samples. $n=7:8:8$. **C**, Flow cytometric analysis of CD8⁺ CD69⁺ T cells in heart samples. $n=7:8:8$. **D**, Flow cytometric analysis of CD4⁺ effector memory T cells (CD4⁺ CD44^{high} CD62L^{low}) in heart samples. $n=5:6:7$. **E**, Flow cytometric analysis of CD8⁺ effector memory T cells (CD8⁺ CD44^{high} CD62L^{low}) in heart samples. $n=5:6:7$. * $P<0.05$, ** $P<0.01$, *** $P<0.001$.

monitoring²³ showed no difference in either systolic or diastolic blood pressure between littermate control and TMRKO mice after AAC (Figure S4), excluding the influence of different pressure to the heart.

T-Cell MR Deficiency Attenuates AAC-Induced Cardiac Dysfunction

Chronic POL eventually leads to cardiac dysfunction. Therefore, we evaluated the effects of TMRKO on cardiac

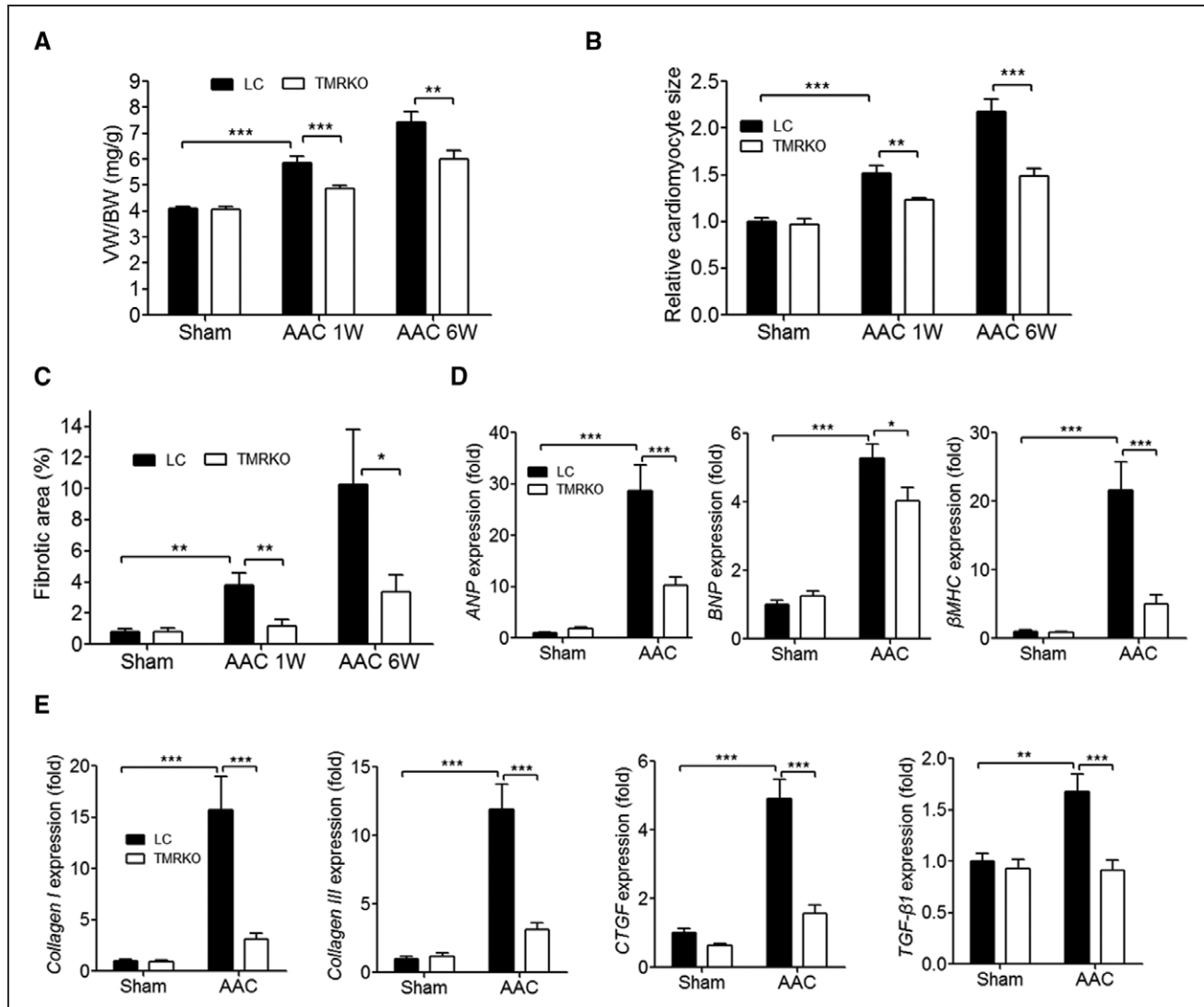


Figure 2. Mineralocorticoid receptor (MR) deficiency attenuates abdominal aortic constriction (AAC)-induced cardiac hypertrophy and fibrosis. **A**, Ventricular weight-to-body weight ratio (VW/BW) of littermate control (LC) and T-cell MR knockout (TMRKO) mice undergone sham operation or AAC for 1 week (1 W) or 6 weeks (6 W). $n=10:8:15:15:10:10$. **B**, Quantification of cardiomyocyte size (cross-sectional area). Results were normalized to those of sham-operated LC group. $n=5:4:6:6:7:6$. **C**, Quantification of fibrotic areas. $n=5:4:6:6:7:6$. **D**, Quantitative reverse transcriptase polymerase chain reaction (QRT-PCR) analysis of hypertrophy-related genes in left ventricles from LC or TMRKO mice 1 week after sham operation or AAC. $n=10:6:15:15$. **E**, QRT-PCR analysis of fibrosis-related genes in left ventricles from LC or TMRKO mice 1 week after sham operation or AAC. $n=10:8:15:15$. $^*P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$. ANP indicates natriuretic peptide A; BNP, natriuretic peptide B; β MHC, cardiac myosin heavy chain β ; CTGF, connective tissue growth factor precursor; and TGF β 1, transforming growth factor β 1.

function using echocardiography. Four weeks after AAC, both end-systolic and end-diastolic left ventricular diameter and volume were augmented in littermate control mice, and these parameters were all attenuated in TMRKO mice (Figure 3A through 3D). Consistently, left ventricular fractional shortening and ejection fraction were both significantly mitigated in TMRKO mice after AAC (Figure 3E and 3F). These results supported that T-cell MR deficiency was beneficial to cardiac function under pathologic conditions.

T-Cell MR Deficiency Decreases AAC-Induced Cardiac Inflammatory Response

Inflammation plays critical roles in pathologic cardiac remodeling.^{29,30} We next determined whether TMRKO affected cardiac inflammation. Accumulation of myeloid cells in the heart was

first analyzed using flow cytometry (Figure S5). Both monocytes/macrophages (CD11b⁺ Ly6G⁻) and neutrophils (CD11b⁺ Ly6G⁺) were decreased in TMRKO hearts 1 week after AAC (Figure 4A). Furthermore, Ly6C^{hi} inflammatory monocytes were decreased in TMRKO mice after AAC (Figure 4B). Immunofluorescence staining further confirmed the diminished cardiac accumulation of neutrophils (Gr-1⁺) and macrophages (CD68⁺) in TMRKO mice (Figure 4C and 4D). Finally, quantitative reverse transcriptase polymerase chain reaction results demonstrated that expression of F4/80 and inflammatory genes, including IL-1 β (interleukin-1 β), RANTES (regulated on activation, normal T-cell expressed and secreted), and MCP-1 (monocyte chemoattractant protein-1), was substantially suppressed in TMRKO hearts after AAC, further supporting the attenuated cardiac inflammatory response (Figure 4E).

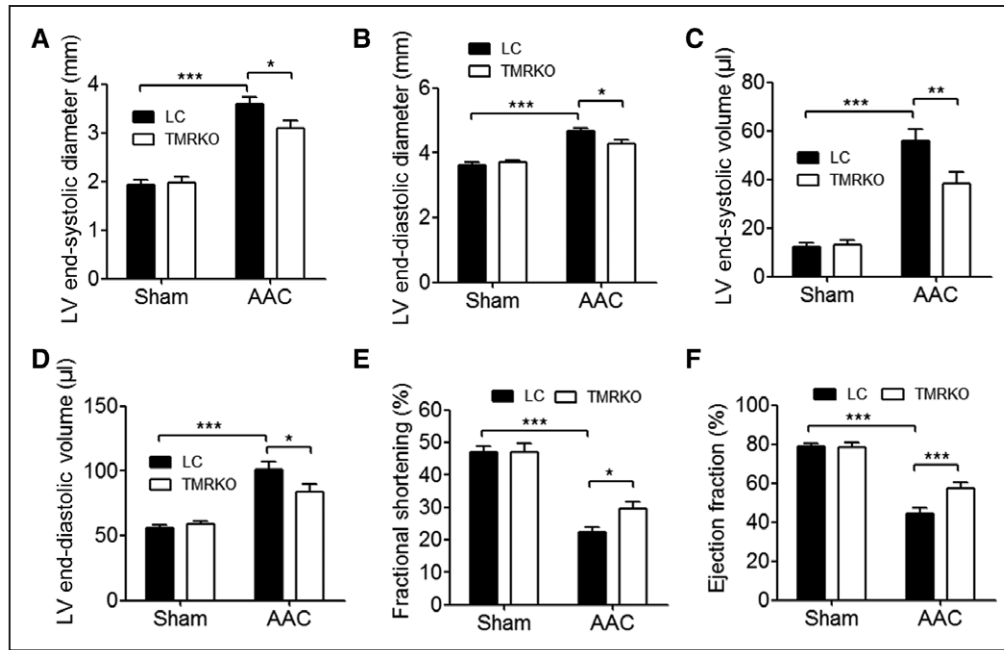


Figure 3. T-cell mineralocorticoid receptor (MR) deficiency attenuates abdominal aortic constriction (AAC)-induced cardiac dysfunction. Left ventricular (LV) end-systolic diameter (A), LV end-diastolic diameter (B), LV end-systolic volume (C), LV end-diastolic volume (D), LV fractional shortening (E), and LV ejection fraction (F) were quantified using echocardiogram measurements. $n=10:8:14:14$. * $P<0.05$, ** $P<0.01$, *** $P<0.001$. LC indicates littermate control; and TMRKO, T-cell MR knockout.

T-Cell MR Deficiency Decreases AAC-Induced T-Cell Accumulation and Activation in the Heart

We next explored how MR deficiency affected T cells in the process of cardiac hypertrophy. Flow cytometric analysis showed that AAC-induced cardiac accumulation of both CD4⁺ T cells and CD8⁺ T cells was markedly mitigated in TMRKO mice compared with littermate control mice (Figure 5A). Numbers of both CD4⁺CD69⁺ and CD8⁺CD69⁺ T cells were significantly decreased in hearts of TMRKO mice after AAC (Figure 5B and 5C). Further, CD4⁺ T_{EM} cells were sharply decreased in heart samples from TMRKO mice after AAC (Figure 5D). There was also a tendency of reduction of CD8⁺ T_{EM} cells in hearts of TMRKO mice after AAC (Figure 5E). In addition, TMRKO significantly suppressed the number of CD4⁺ IFN γ ⁺ T cells in hypertrophied hearts (Figure S6A) and to a less extent, the number of CD8⁺ IFN γ ⁺ T cells (Figure S6B). These results suggested that the activation of T cells, especially CD4⁺ T cells, was downregulated by T-cell MR deficiency in the setting of pathologic cardiac hypertrophy.

MR Regulates T-Cell Activation In Vitro

Previous data have shown that CD4⁺ T cells, rather than CD8⁺ T cells, play a dominant role during POL-induced cardiac hypertrophy and dysfunction.⁷ Therefore, we paid attention particularly to CD4⁺ T cell in our experiment. Elevated expression of IL-2 and increased expression of cell surface molecules, such as CD44, CD69, and CD25, are important markers of T-cell activation.^{31–33} Quantitative reverse transcriptase polymerase chain reaction results showed that MR antagonist spironolactone effectively inhibited the expression of IL-2 in naive splenic CD4⁺ T cells stimulated by anti-CD3 antibodies (Figure S7A). Flow cytometric analysis demonstrated that spironolactone repressed anti-CD3-induced elevation of

CD4⁺CD44⁺ population (Figure S7B). Expression of CD69 and CD25 in CD4⁺ T cells was also suppressed by spironolactone (Figure S7C and S7D). Nonetheless, spironolactone also decreased the expression of CD44 and CD69 in CD8⁺ T cells (Figure S8).

Consistently, TMRKO largely recapitulated the effects of spironolactone on the expression of IL-2 (Figure 6A) and the percentage of CD4⁺CD44⁺, CD4⁺CD69⁺, and CD4⁺CD25⁺ populations in naive CD4⁺ T cells under the stimulation of anti-CD3 antibodies (Figure 6B through 6D). Furthermore, TMRKO markedly inhibited the secretion of inflammatory cytokines, including IFN γ and IL-6, in activated CD4⁺ T cells (Figure 6E). During T-cell activation, NFATc2 (nuclear factor of activated T cells, cytoplasmic 2) is dephosphorylated and translocated into nucleus to initiate IL-2 transcription.^{34,35} Western blotting results showed that TMRKO noticeably decreased the amount of dephosphorylated NFATc2 after stimulation with anti-CD3 antibodies for 1 and 2 hours (Figure 6F).

On the contrary, overexpression of MR in naive CD4⁺ T cells using lentivirus (Figure S9A) significantly upregulated the expression of IL-2 as demonstrated by quantitative reverse transcriptase polymerase chain reaction (Figure S9B) and the percentage of CD4⁺CD44⁺ and CD4⁺CD69⁺ population as demonstrated by flow cytometric analysis (Figure S9C and S9D).

To further confirm our results in fully activated T cells, MR antagonist-treated, TMRKO, and MR-overexpressed CD4⁺ T cells were stimulated with the combination of anti-CD3 and anti-CD28 antibodies. Consistently, MR inhibition and TMRKO downregulated, whereas overexpression of MR upregulated IL-2, CD44, and CD69 (Figure S10). Flow cytometric analysis demonstrated that TMRKO did not affect proliferation of CD4⁺ T cells (Figure S11).

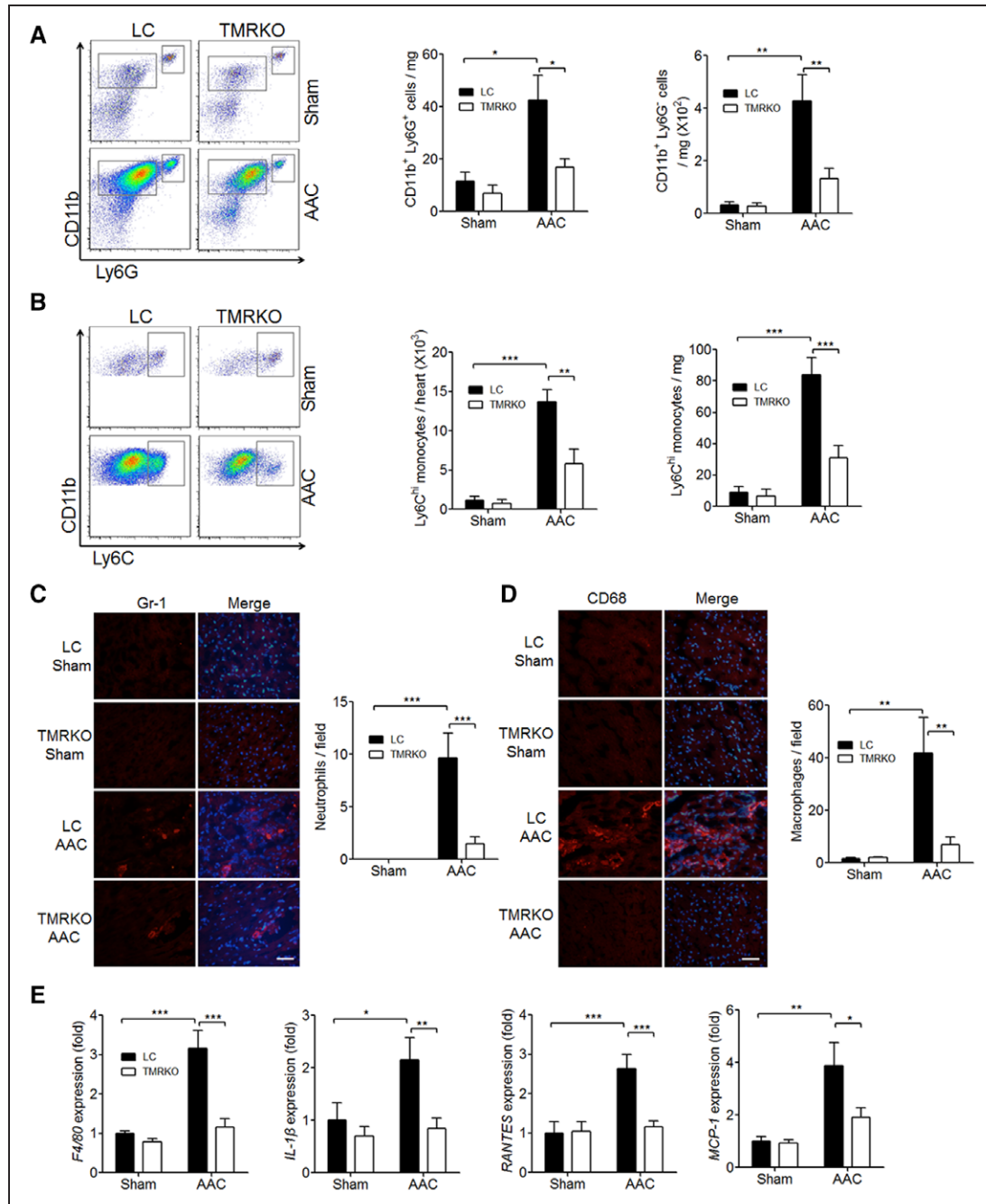


Figure 4. T-cell mineralocorticoid receptor (MR) deficiency decreases abdominal aortic constriction (AAC)-induced cardiac inflammatory response. **A**, Flow cytometric analysis of myeloid cells in heart samples from littermate control (LC) and T-cell MR knockout (TMRKO) mice undergone sham operation or AAC. $n=6:5:13:13$. **B**, Flow cytometric analysis of inflammatory monocytes (Ly6C^{hi}) in heart samples. $n=6:5:13:13$. **C**, Immunofluorescence analysis of Gr-1⁺ cells in sections of heart samples. $n=5:5:6:6$. **D**, Immunofluorescence analysis of CD68⁺ cells in sections of heart samples. $n=5:5:6:6$. **E**, Quantitative reverse transcriptase polymerase chain reaction (QRT-PCR) analysis of inflammatory genes in left ventricles. F4/80 (Emr1) indicates EGF-like module containing, mucin-like, hormone receptor-like sequence 1; IL-1β, interleukin-1β; MCP-1, monocyte chemoattractant protein-1; and RANTES, regulated on activation, normal T-cell expressed and secreted. $n=10:8:14:15$. Scale bars: 50 μm. * $P<0.05$, ** $P<0.01$, *** $P<0.001$.

Discussion

Although functions of MR in several other cell types have been elucidated in pathologic cardiac hypertrophy and heart failure,^{15–17,19,36–38} the roles of MR in T cells have not been illuminated. Through this study, we demonstrated that eplerenone and TMRKO attenuated POL-induced cardiac remodeling and dysfunction in parallel with attenuated cardiac inflammation,

as well as decreased T-cell accumulation and activation in the heart. Moreover, in vitro results illustrated direct regulation of T-cell activation by MR.

This study implies that MR blockade in T cells is a feasible approach to treat pathologic cardiac hypertrophy and heart failure. MR deficiency in T cells was sufficient to suppress POL-induced cardiac hypertrophy, cardiac fibrosis,

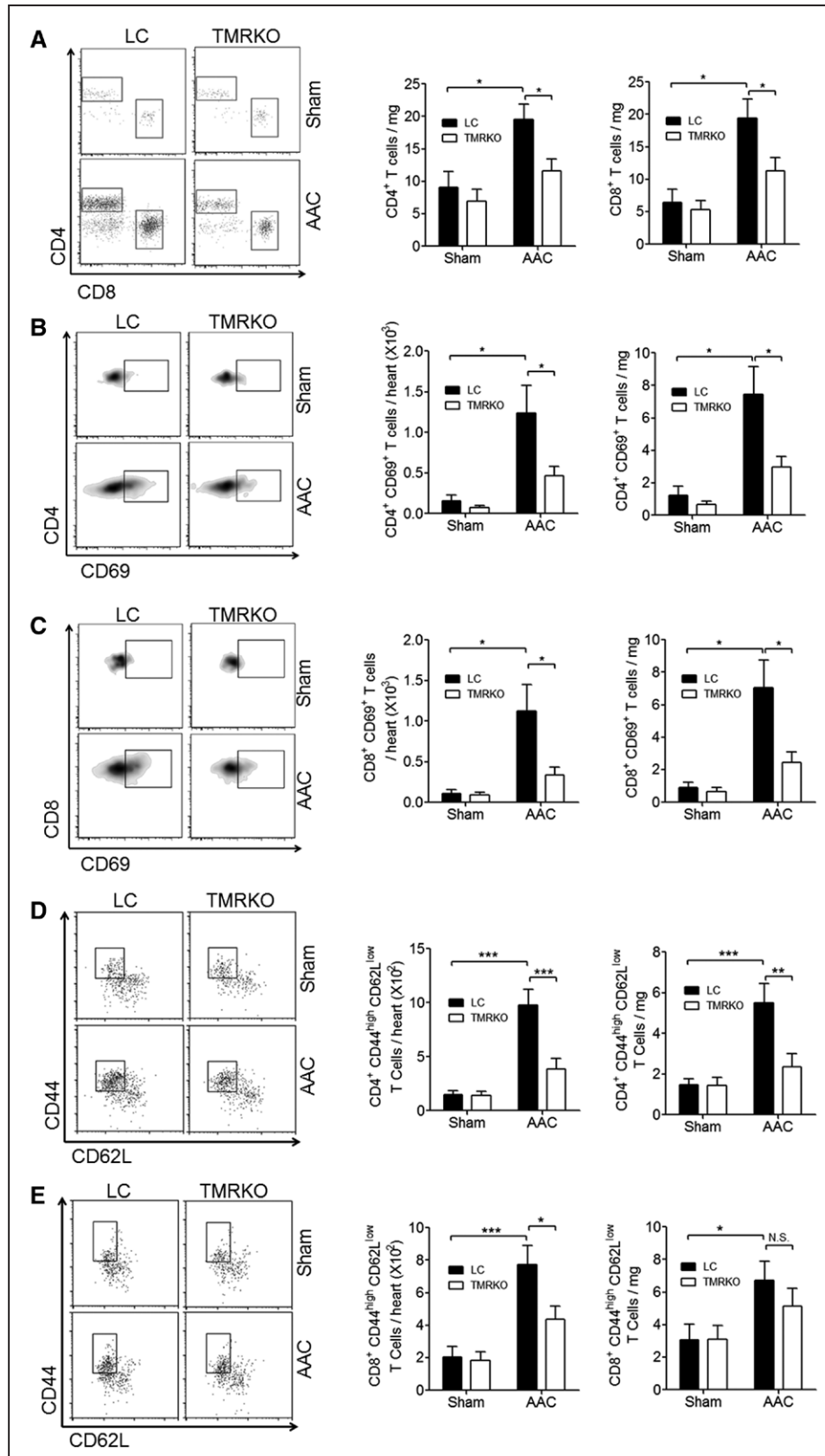


Figure 5. T-cell mineralocorticoid receptor (MR) deficiency decreases abdominal aortic constriction (AAC)-induced T-cell accumulation and activation in the heart. **A**, Flow cytometric analysis of T cells in heart samples from littermate control (LC) and T-cell MR knockout (TMRKO) mice undergoing sham operation or AAC. $n=5:5:15:14$. **B**, Flow cytometric analysis of CD4⁺ CD69⁺ T cells in heart samples. $n=5:5:13:12$. **C**, Flow cytometric analysis of CD8⁺ CD69⁺ T cells in heart samples. $n=5:5:13:12$. **D**, Flow cytometric analysis of CD4⁺ effector memory T cells (CD4⁺ CD44^{high} CD62L^{low}) in heart samples. $n=8:8:10:10$. **E**, Flow cytometric analysis of CD8⁺ effector memory T cells (CD8⁺ CD44^{high} CD62L^{low}) in heart samples. $n=8:8:10:10$. * $P<0.05$, ** $P<0.01$, *** $P<0.001$.

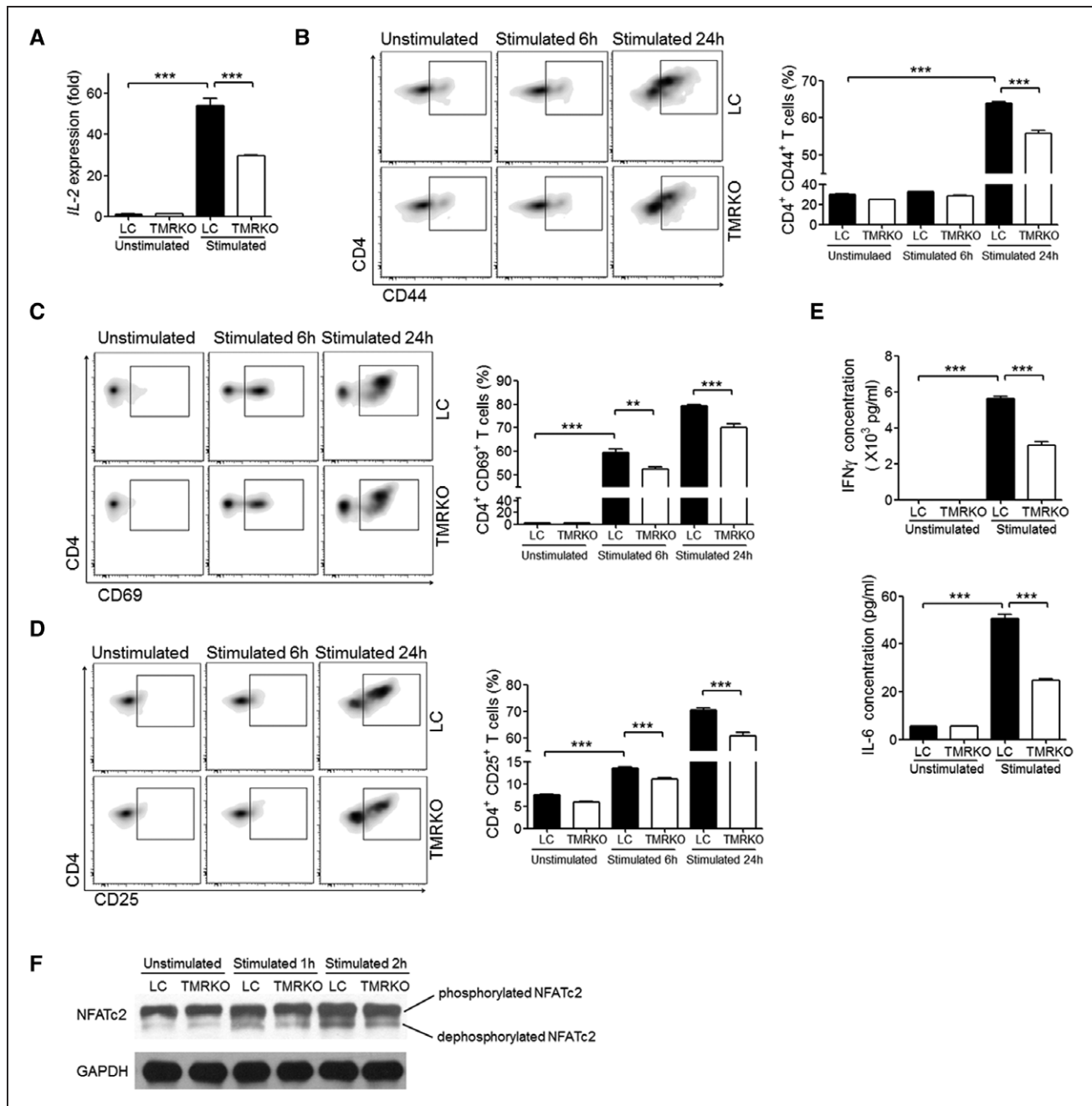


Figure 6. Mineralocorticoid receptor (MR) regulates T-cell activation in vitro. **A**, Quantitative reverse transcriptase polymerase chain reaction (QRT-PCR) analysis of IL-2 (interleukin-2) gene expression in naive CD4⁺ T cells isolated from littermate control (LC) and T-cell MR knockout (TMRKO) mice without stimulation (unstimulated) or stimulated with anti-CD3 for 24 h. **B**, Flow cytometric analysis of CD44 in naive CD4⁺ T cells isolated from LC and TMRKO mice. **C**, Flow cytometric analysis of CD69 in naive CD4⁺ T cells. **D**, Flow cytometric analysis of CD25 in naive CD4⁺ T cells. **E**, Enzyme-linked immunosorbent assay (ELISA) of IFN γ (interferon- γ) and IL-6 in culture media from naive CD4⁺ T cells. **F**, Western blotting analysis of NFATc2 (nuclear factor of activated T cells, cytoplasmic 2) in naive CD4⁺ T cells. Data represent 3 independent experiments. ** P <0.01, *** P <0.001.

and cardiac dysfunction, as well as cardiac inflammation in mice. Particularly, TMRKO completely abrogated parts of the phenotype 1 week after POL, indicating that MR in T cells may be more important than MR in other cellular compartments in the early stage of cardiac remodeling. MR deletion in other cell types, such as cardiomyocytes, also manifests protection against cardiac remodeling, mostly in the later stage rather than the early stage of the process.^{14,15} It is conceivable to target MR in T cells specifically

to circumvent the side effects of systemic MR blockade. An early study engineered a chimeric major histocompatibility complex class II to deliver doxorubicin to CD4⁺ T cells through specific binding of T-cell receptor.³⁹ Similar approach could be exploited to deliver MR antagonists to specifically target T cells and treat pathologic cardiac hypertrophy and heart failure with fewer side effects in expectation. Higher dosage is also plausible when better efficacy is desired.

We have provided evidence to show the direct role of T-cell MR in regulation of T-cell activation, particularly in the setting of pathologic cardiac remodeling. MR signaling has been shown to regulate the number of circulating T cells in human subjects.⁴⁰ Spironolactone decreases the expression of IL-17 and increases that of forkhead box P3 in a rat model of hypertension, indicating that MR blockade downregulates Th17, while it upregulates Treg polarization.⁴¹ Intriguingly, earlier data suggest that aldosterone and spironolactone modulate the function of dendritic cells, which affect T-cell activation and polarization.⁴² However, the direct role of MR in CD4⁺ T cells has not been vigorously investigated. Our in vivo results illustrated that MR deficiency in T cells markedly suppressed the accumulation and activation of T cells in hypertrophied hearts. In vitro results further elaborated a direct regulatory role of MR on activation of CD4⁺ T cells, using specific knockout and direct overexpression of MR in T cells in addition to MR antagonism. Moreover, our data indicated that NFATc2 was a connecting point mediating the functions of MR in CD4⁺ T cells, although the molecular machinery needed further exploration.

Our data have also revealed that inflammation is an important link between MR signaling in T cells and pathologic cardiac remodeling. Inflammation is at the center stage of pathologic cardiac remodeling and heart failure.^{29,30} Previous reports have shown that lessened T-cell activation is correlated with diminished cardiac inflammation in the setting of POL.^{5,6} We presented that TMRKO mice manifested reduced cardiac inflammation in parallel with improved cardiac remodeling, as well as decreased T-cell accumulation and activation in the heart after POL. Particularly, cardiac expression levels of inflammatory cytokines, as well as accumulation of neutrophils and monocytes/macrophages, were both suppressed by T-cell MR deficiency. These data together supported the importance of inflammation in mediating the impacts of T-cell MR signaling.

MR deficiency and its influence on T-cell activation may modulate interactions between T cells and myeloid cells, contributing to the attenuated cardiac inflammation and ultimately the improved cardiac remodeling and dysfunction. Interactions between T cells and myeloid cells are essential in modulating inflammatory tissue microenvironments. CD8⁺ T cells infiltrate preceding accumulation of macrophages in inflamed adipose tissue and play critical roles in obesity and insulin resistance.⁴³ In spontaneous autoimmune myocarditis, CD4⁺ T cells are assumed to orchestrate the cardiac pathology through recruiting and activating macrophages.⁴⁴ A more recent study has exemplified the importance of reciprocal interactions between T cells and macrophages in angiotensin II-induced cardiac inflammation and remodeling.⁴⁵ It would be reasonable that MR deficiency in T cells modulated interactions between T cells and myeloid cells in the setting of POL. However, the exact mechanisms remain to be interrogated. Either direct or cytokine-facilitated interactions between T cells and myeloid cells may mediate the effects of MR deficiency and T-cell activation on infiltration and phenotypic alterations of macrophages and neutrophils and consequently on cardiac inflammation, as well as ultimately on cardiac remodeling and dysfunction.

Perspectives

We have revealed that MR blockade, particularly in T cells, ameliorates AAC-induced cardiac hypertrophy and dysfunction. MR directly regulates T-cell activation, reflecting that MR blockade decreases activation and accumulation of T cells in the heart, likely contributing to the suppressed inflammation and cardiac protection of MR antagonism or deficiency. These results support that T-cell MR may at least partially mediate the beneficial effects of MR antagonists. Furthermore, the study provides knowledge basis for targeting MR in T cells specifically to circumvent side effects of systemic MR blockade and achieve better outcomes for treating pathologic cardiac hypertrophy and heart failure.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Both genetic deficiency and pharmacologic inhibition of mineralocorticoid receptor (MR) attenuate cardiac remodeling and accumulation and activation of T cells in the heart. MR directly regulates T-cell activation.

What Is Relevant?

- MR antagonists are widely used for patients with heart failure. Our findings indicate that MR in T cells has detrimental effects during pathologic cardiac hypertrophy and dysfunction. Targeting MR in T cells specifically may be a feasible approach for treating patients with heart failure.

Summary

Pathologic cardiac hypertrophy is a major cause of heart failure. Targeting T cells represents a new approach for treating patho-

logic cardiac hypertrophy and heart failure. In the current study, we investigate whether MR influences T-cell activation to regulate pathologic cardiac hypertrophy. We illustrate that MR deficiency in T cells attenuates pressure overload–induced cardiac hypertrophy, fibrosis, dysfunction, and inflammation. Both MR deficiency and antagonists reduce T-cell accumulation and activation in hypertrophied hearts. In vitro, both MR antagonism and deficiency suppress activation of T cells, whereas MR overexpression elevates activation of T cells. These findings have revealed novel functions of MR in modulating T-cell activation and in regulating pathologic cardiac hypertrophy. It is conceivable to specifically target MR in T cells and to treat pathologic cardiac hypertrophy and heart failure more effectively.