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REVIEW ARTICLE

The multifaceted functions of mineralocorticoid receptor in cardiometabolic disease

Jian-Yong Sun[1,2], Yong-Li Wang[3], Hong Zhu[1,2], and Sheng-Zhong Duan[1,2]*

[1]Laboratory of Oral Microbiota and Systemic Diseases, Shanghai Ninth People's Hospital, College of Stomatology, Shanghai Jiao Tong University School of Medicine, Shanghai 200125, China

[2]National Centre for Stomatology; National Clinical Research Center for Oral Diseases; Shanghai Key Laboratory of Stomatology, Shanghai 200011, China

[3]Department of Cardiology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China

Abstract

Cardiometabolic diseases (CMDs), which cause 31% of all global deaths, are one of the greatest public health challenges. Mineralocorticoid receptor (MR), as a key nuclear transcription factor, is an important drug target for the treatment of CMDs. It is known that MR is expressed in almost all tissues and organs involved in cardiovascular homeostasis, including immune tissue, adipose tissue, brain, heart, kidney, and blood vessels. In the pathophysiology of CMDs, MR exerts different functions in different tissues and cells. This review summarizes the roles of MR in various cell types and discusses the molecular mechanisms through which MR exerts it functions in CMDs.

Keywords: Cardiometabolic diseases; Mineralocorticoid receptor; Mineralocorticoid receptor antagonist

***Corresponding author:**
Sheng-Zhong Duan
(duansz@shsmu.edu.cn)

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1. Introduction

Cardiometabolic diseases (CMDs) remain the leading cause of morbidity and mortality worldwide[1]. CMDs contain a constellation of cardiovascular diseases (CVDs), including coronary heart disease, stroke, hypertension, and associated metabolic disorders, such as obesity and diabetes[1,2]. The incidence of classical risk factors for CMDs such as smoking, high blood pressure, and hypercholesterolemia has decreased over the past few decades[2]. However, the rate of obesity and the prevalence of type 2 diabetes have markedly increased[2,3]. This changing disease pattern poses a huge challenge to the treatment of CMDs. Although there is a growing number of drugs that target classical cardiovascular risk factors, such as hypertension and hyperlipidemia, current treatment regimens do not prevent most cardiovascular events[4]. Therefore, it is necessary to further study the pathophysiological mechanism of CMDs to identify new targets for personalized therapy.

Mineralocorticoid receptor (MR) is a member of the nuclear receptor superfamily[5]. MR is involved in transcriptional regulation and plays important roles in CMDs[5-7]. The steroid hormone aldosterone is a classical MR ligand that regulates blood pressure and promotes sodium retention in the kidney[8,9]. An increasing number of clinical

trials have shown that the activation of aldosterone/MR signaling increases the risk and adverse clinical outcomes in patients with hypertension, myocardial infarction (MI), heart failure (HF), and stroke[10,11]. Experimental evidence has demonstrated that MR activation by aldosterone induces oxidative stress, inflammation, and fibrosis, all of which contribute to the progression of CMDs[12,13]. However, aldosterone is not the only ligand for MR. Glucocorticoids have similar affinity and specificity for MR[14]. In certain cells, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) restricts the binding of glucocorticoids to MR by converting endogenous glucocorticoids to metabolites that have poor affinity for MR[7]. Conversely, the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) converts the inactive dehydrogenated form of glucocorticoids into active form[7,15]. The ligand-independent activation of MR has also been investigated. Rac1, a small GTPase belonging to the Rho family, can activate MR, leading to nuclear translocation in renal and cardiac diseases[16,17]. It has been reported that high glucose activates the transcriptional activity of MR through protein kinase C β signaling[18] and high salt causes renal MR activation through the induction of oxidative stress and exacerbates renal injury[19].

It has been clearly established that MR is expressed and functional in extra-renal tissues, such as brain, liver, lung, colon, bone, heart, vasculature, and immune system[20,21]. The role of MR varies in different cell types. For example, monocyte/macrophage MR deficiency affects macrophage polarization and vascular remodeling[22,23]. The deletion of vascular smooth muscle MR ameliorates aging- or angiotensin (Ang) II-induced hypertension in mice[24]. Although the overexpression of MR in endothelial cells promotes vasoconstriction and leads to hypertension[25], the deletion of MR has no effect on blood pressure[25,26]. MR knockout in T cells alleviates renal and vascular lesions and reduces Ang II-induced hypertension[27]. Therefore, elucidating the regulatory mechanisms of MR in different cell types may provide new strategies to treat CMDs.

This review summarizes the effects of MR in different cell types on the pathological process of CMDs and specifically highlights the expression and function of MR in immune cells, adipocytes, vascular cells, and myocardial cells. We also discuss the application and challenges of MR antagonists in the treatment of CMDs, to highlight promising novel therapeutic strategies.

2. Immune cell MR and CMDs

Inflammation and immune cells are closely related to the pathogenesis of CMDs[5,28-30]. The previous studies have shown that aldosterone activates the immune system to promote the expression of inflammatory cytokines and the recruitment of immune cells, both of which contribute to tissue damage and impaired healing in CMDs[30]. MR is expressed in most immune cells, including monocytes/macrophages, dendritic cells (DCs), T cells, and B cells[30]. Immune cell MR is involved in the pathological processes of many cardiovascular and metabolic diseases.

2.1. Macrophage MR and CMDs

2.1.1. Role of macrophage MR in atherosclerosis

Macrophages are the main immune cells in atherosclerotic plaques and are closely related to the pathological process of atherosclerosis[31]. MR activation by aldosterone increases atherosclerosis plaque size and macrophage numbers in the plaques[32]. Conversely, MR inactivation by eplerenone decreases macrophage oxidative stress and improves atherosclerosis[33]. Recent studies have suggested that macrophage MR plays a major role in atherosclerosis[34,35]. MR deficiency in macrophages decreases plaque size in early- and late-stage atherosclerosis through different mechanisms. In the early stage of atherogenesis, MR deficiency downregulates the expression of P-selectin glycoprotein ligand-1 (a critical mediator of leukocyte rolling) in macrophages and suppresses leukocyte trafficking to reduce inflammation in atherosclerotic plaques[35]. Macrophage-specific MR deletion inhibits macrophage foam cell formation and increases the phagocytic and efferocytosis capacities of macrophages in a mouse model of late-stage atherosclerosis[34].

2.1.2. Role of macrophage MR in MI

Macrophage MR deficiency has been shown to improve cardiac function and decrease the size of infarct scar following MI, with enhanced infarct neovascularization and scar maturation[36]. Mechanistically, MR deletion in macrophages promotes post-MI cardiac repair by enhancing neutrophil efferocytosis, suppressing free radical formation, and regulating fibroblast activation status[36]. Targeting macrophages with eplerenone-containing liposome protects against cardiac dysfunction and adverse cardiac remodeling following MI, thus suggesting that the targeted delivery of MR antagonists to macrophages post-MI could be a novel strategy to prevent the side effects of MR antagonists on electrolytes[36].

2.1.3. Role of macrophage MR in hypertension

The role of macrophage MR has also been investigated in different models of hypertension[22,37,38]. In deoxycorticosterone acetate (DOCA)/salt- and low-dose treatment of N^G-nitro-L-arginine methyl ester (L-NAME)/salt-induced hypertension models, the deletion of macrophage MR reduces systolic blood pressure, diminishes cardiac fibrosis, and inhibits the expression of pro-

inflammatory factors, with no change in the recruitment of macrophages to the heart[37,38]. In an L-NAME/AngII-induced hypertension model, MR deficiency in macrophages not only protects against cardiac hypertrophy, fibrosis, and vascular damage, but also decreases macrophage recruitment to the heart[22]. Intriguingly, in this model, the blood pressure of macrophage MR deficient mice was slightly elevated[22]. Mechanistically, MR deficiency in macrophages inhibits the expression of M1 markers and increases the expression of alternatively activated M2 markers[22]. In addition, MR deficiency synergizes with interleukin (IL)-4 to facilitate the polarization of macrophages to M2 phenotype signaling[22] (Figure 1).

2.1.4. Role of macrophage MR in arterial injury

Macrophage MR is also involved in the repair process of arterial injury (AI). MR deficiency in macrophages inhibits AI-induced neointimal hyperplasia by inhibiting macrophage accumulation and vascular inflammation[23]. At the molecular level, MR deletion promotes the polarization of macrophages to an anti-inflammatory phenotype by suppressing activator protein 1 (AP-1)/nuclear factor κB (NF-κB) signaling pathways in macrophages[23] (Figure 1). MR deficiency also inhibits the migration and proliferation of macrophages both *in vivo* and *in vitro*[23]. However, further research is required to determine the underlying mechanism.

2.1.5. Role of macrophage MR in obesity and diabetes

Macrophages are closely related to obesity and type 2 diabetes mellitus (T2DM)[39]. MR antagonists have been shown to improve hepatic steatosis and insulin resistance in obese animal models[40,41]. A deficiency in macrophage MR improves glucose intolerance, insulin resistance, and hepatic steatosis in obese mice[42], implying that macrophage MR plays an important role in obesity and T2DM. Mechanistically, in the presence of estrogen, MR deletion directly upregulates estrogen receptor alpha (ERα) expression in macrophages and enhance the secretion of hepatocyte growth factor (HGF)[42]. Subsequently, the macrophage-secreted HGF phosphorylates and activates hepatocyte Met, which mediates a decrease in lipid accumulation and an increase in insulin signaling in hepatocytes, thus improving hepatic steatosis and insulin resistance in obese mice[42] (Figure 1). These results suggest that the MR/ERα/HGF/Met axis is a potentially important metabolic pathway linking macrophages to hepatocytes.

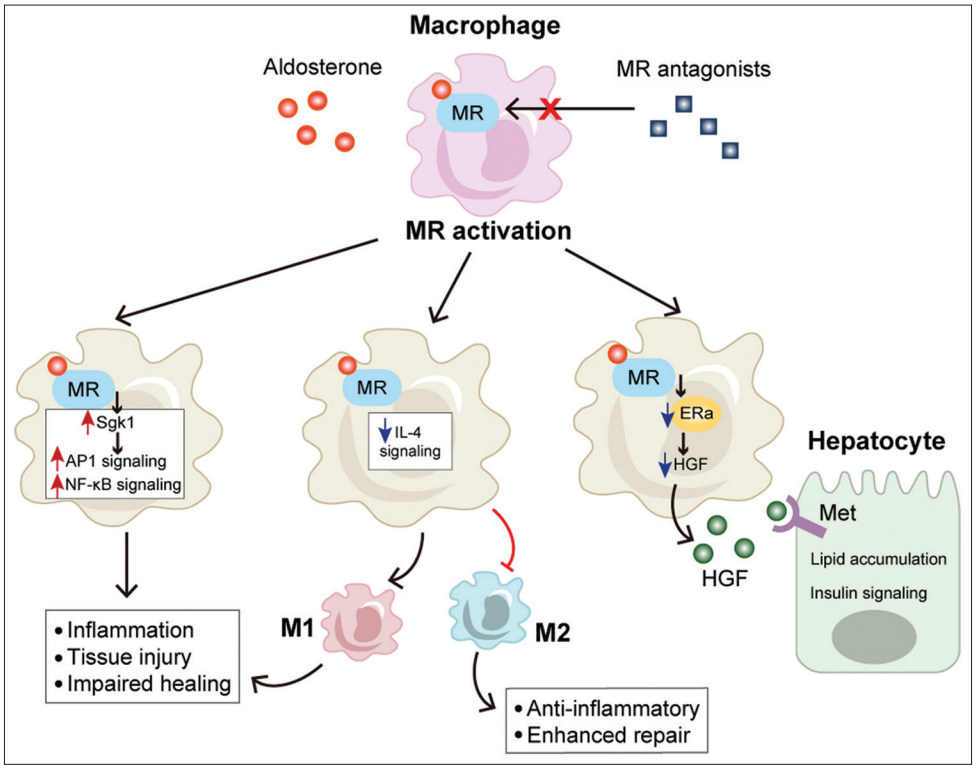

Figure 1. Role of mineralocorticoid receptor (MR) in macrophages. MR activation in macrophages promotes the polarization of macrophages to a proinflammatory phenotype by activating activator protein 1/nuclear factor κB signaling pathway, which leads to excessive inflammation, tissue injury, and impaired healing. In addition, MR activation suppresses interleukin-4 signaling and promotes macrophage polarization to M1 phenotype. In Kupffer cells, the resident macrophages in the liver, MR affects the secretion of hepatocyte growth factor (HGF) by regulating estrogen receptor alpha expression. HGF could phosphorylate and activate hepatocyte Met, which mediates lipid accumulation and insulin signaling in hepatocytes.

2.2. Role of DC MR in hypertension

DCs are activated and increased in the secondary lymphoid tissue of hypertensive mice treated with Ang II infusion or DOCA salt[43]. The specific ablation of DCs (CD11c-expressing cells) prevents the development of hypertension as a result of Ang II infusion[44,45]. MR is also expressed and functional in DCs[46]. MR activation in DCs promotes the differentiation of T cells into pro-inflammatory Th1 and Th17 phenotypes and decreases the proportion of regulatory T cells (Tregs) (Figure 2). This imbalance between T helper cells and Tregs contributes to the pathogenesis of hypertension and its associated complications[47,48]. Further experiments have shown that aldosterone pretreatment activates DCs, promotes the expression of DC maturation markers CD80 and CD86, and induces DCs to secrete cytokines such as IL-6 and IL-23, thereby activating $CD4^+$ and $CD8^+$ T cells[46]. These activated T cells then migrate to the kidney and vasculature, producing interferon gamma (IFNγ) and IL-17A and exacerbating hypertension[49] (Figure 2). Spironolactone, an MR antagonist, effectively inhibits DC activation, T cell immunity, and the development of hypertension[30,46].

Araos *et al.* have provided information concerning the downstream mechanisms of DC MR activation in a nephrectomy-aldosterone-salt model of hypertension[50]. MR stimulation in DCs favors neutrophil gelatinase-associated lipocalin (NGAL) and IL-23 expression, which are involved in the development of fibrosis and Th17 response, respectively[50] (Figure 2). NGAL has been identified as a specific target of MR in cardiovascular cells[50-52]. The specific knockout of DC NGAL can effectively inhibit MR-dependent T cell activation and inflammatory response[50].

2.3. T cell MR and CMDs

2.3.1. Role of T cell MR in hypertension

The previous animal models and clinical studies have demonstrated that T cells play a key role in mediating renal and vascular inflammation and hypertension[53,54]. The role of T cell MR in hypertension has been investigated. In Ang II-infused mice, the deletion of MR in T cells strikingly decreases both systolic and diastolic blood pressures and attenuates renal and vascular damages[27]. In contrast, the overexpression of MR in T cells increases blood pressure in response to Ang II infusion[27]. Mechanically, MR in T cells, particularly $CD8^+$ T cells, interacts with transcription factors nuclear factor of activated T cells 1 (NFAT1) and AP-1 to regulate IFNγ production, and ultimately influences blood pressure[27] (Figure 2). Consistently, eplerenone, which is also an MR antagonist, attenuates AngII-induced hypertension and decreases IFNγ expression in $CD8^+$ T cells[27]. Other studies have shown that T cell MR is involved in the regulation of renal fibrosis and blood pressure in DOCA/salt-induced hypertension model by regulating the expression of C-X-C chemokine receptor type 4 (CXCR4)[55,56]. As reported, mineralocorticoid excess stimulates the accumulation of T cells in the kidney, which is significantly blunted by CXCR4

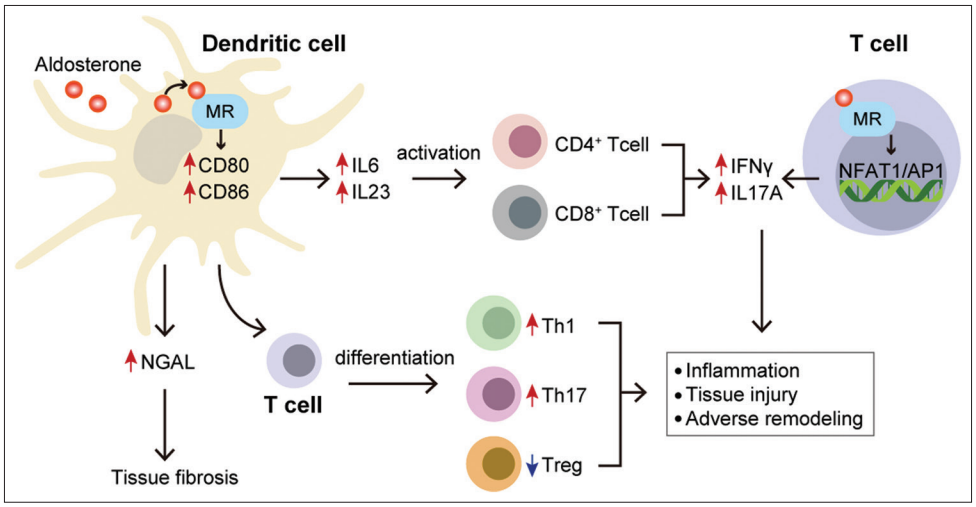

Figure 2. Role of mineralocorticoid receptor (MR) in dendritic cells (DCs) and T cells. MR activation in DCs promotes the differentiation of T cells into pro-inflammatory Th1 and Th17 phenotypes as well as decreases the proportion of regulatory T cells (Tregs). Moreover, MR activation enhances the expression of DC maturation markers CD80 and CD86 as well as induces DCs to secrete cytokines, such as interleukin (IL)-6 and IL-23, thereby activating $CD4^+$ and $CD8^+$ T cells. Activated T cells increase the expression of pro-inflammatory cytokines Interferon gamma (IFNγ) and IL-17A, both of which lead to tissue inflammation and injury. In addition, MR activation in DCs favors the expression of neutrophil gelatinase-associated lipocalin, which contributes to the development of fibrosis. In T cells, MR interacts with transcription factors nuclear factor of activated T cells 1 and activator protein 1 to regulate IFNγ production. The excessive inflammation eventually leads to tissue injury and adverse remodeling.

inhibition and MR antagonist[56]. These data suggest that T cell MR regulates the expression of chemokine receptors and inflammatory factors, affecting T cell aggregation and the level of inflammation, respectively, thus affecting blood pressure.

2.3.2. Role of T cell MR in cardiac remodeling

The previous study has shown that T cell MR is also involved in the pathological process of myocardial remodeling[17]. In a mouse model of abdominal aortic contraction (AAC)-induced cardiac hypertrophy, T cell MR deficiency reduces cardiac hypertrophy, fibrosis, inflammation, and dysfunction[57]. Consistently, MR antagonists inhibit cardiac hypertrophy and fibrosis, induced by AAC, and reduce the accumulation and activation of $CD4^+$ and $CD8^+$ T cells in mouse heart[57]. Mechanistically, T cell MR deletion could inhibit the expression of surface molecule CD44, CD69, and CD25, which are all important markers of T cell activation, suggesting that MR could directly regulate T cell activation[57]. Moreover, the deficiency of T cell MR suppresses the expression of IL-2 most likely by decreasing the amount of dephosphorylated NFATc2[57]. These results support that T cell MR contributes to cardiac remodeling and dysfunction following pressure load.

2.4. B cell MR

B cells are adaptive immune cells, and their main functions include antibody generation, antigen presentation, T cell co-stimulation, and cytokine production[58]. B cells have been progressively recognized as modulators of both adaptive and innate immune responses and for their role in the pathogenesis of CMDs, such as MI, HF, vascular disease, and obesity-associated metabolic disease[58,59]. MR expression has been found in B cells[30]. However, it is still unclear whether B cell MR plays a role in CMDs and whether MR regulates B cell function.

3. Vascular cell MR and CMDs

3.1. Role of MR in endothelial cells

3.1.1. Role of endothelial cell MR in atherosclerosis

Atherosclerosis, a chronic inflammatory disease, is a risk factor for many other CVDs[60]. Endothelial cells (ECs) play an important role in the pathological process of atherosclerosis[61]. In response to cardiovascular risk factors, injury to the vascular endothelium occurs, and a dysfunctional endothelium in turn promotes the adhesion and migration of white blood cells to vascular walls[61]. On the other hand, dysfunctional ECs promote vascular inflammation by expressing surface adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial selectin[62,63] (Figure 3). Caprio *et al.* have shown that aldosterone-activated MR increases ICAM-1 expression in primary human ECs and promotes leukocyte adhesion *in vitro*[64]. Further experiments have shown that ICAM-1 deletion in ECs alleviated vascular inflammation and plaque areas in a mouse model of aldosterone-induced atherosclerosis and MR directly regulated the gene expression of ICAM-1 in ECs[65], suggesting that MR plays a role in atherosclerosis disease through ICAM-1. Moss *et al.* have demonstrated that the deficiency of EC MR did not affect the plaque size or composition in a mouse atherosclerosis model[66]. However, plaque inflammation was significantly ameliorated in EC MR knockout mice[66]. These experimental results imply that EC MR mediates vascular inflammation in atherosclerosis.

3.1.2. Role of endothelial cell MR in hypertension

The role of vascular EC MR in blood pressure regulation has also been explored. Nguyen Dinh Cat *et al.* have demonstrated that the overexpression of MR in ECs elevates blood pressure at baseline and in response to endothelin 1 or Ang II infusion as well as enhances the contractile response of mesenteric arteries to vasoconstrictors without affecting the vascular morphology[25]. In contrast, MR deletion in ECs has no effect on blood pressure at baseline or in DOCA/salt- or Ang II-induced mouse models[67,68]. However, EC MR deficiency has shown to ameliorate cardiac remodeling by inhibiting the recruitment of macrophages and reducing the expression of myocardial pro-inflammatory factors in a mouse model of DOCA/salt-induced hypertension[67,68]. Meanwhile, EC MR deficiency has shown no effect on renal fibrosis, glomerular injury, proteinuria, or inflammation in a DOCA/salt-induced model[67-69]. Remarkably, MR deletion in ECs protects DOCA salt-induced aortic endothelial dysfunction but has no effect on the mesenteric artery[68]. In Ang II-induced hypertension, EC MR deletion improves the dilatation function of mesenteric (but not coronary) artery[26]. These data suggest that EC MR is involved in regulating vasoconstriction in a vascular bed-specific manner.

3.1.3. Role of endothelial cell MR in angiogenesis

EC MR also plays a role in angiogenesis. Zheng *et al.* have demonstrated that the deletion of EC MR promotes blood flow recovery and increases blood vessel density in ischemic limbs in a mouse model of hindlimb ischemia[70]. Moreover, MR knockout increases angiogenic potential, migration capacity, and EC proliferation *in vitro*[70]. Mechanistically, MR affects endothelial cell function by inhibiting signal transducer and activator of transcription 3 (STAT3) expression by binding to CCAAT enhancer-binding protein beta (C/EBPβ)[70] (Figure 3). Interestingly,

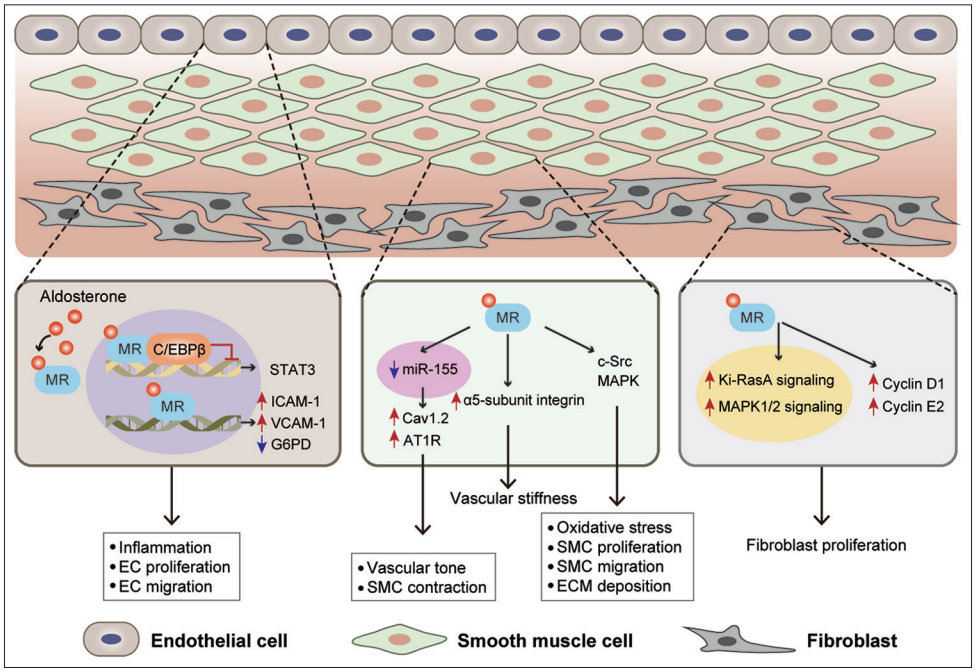

Figure 3. Role of mineralocorticoid receptor (MR) in vascular cells. In endothelial cells (ECs), MR activation promotes vascular inflammation by enhancing the expression of surface adhesion molecules, including intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and inhibiting the expression of glucose-6-phosphate dehydrogenase. In addition, MR affects endothelial cell proliferation and migration by inhibiting the expression of signal transducer and activator of transcription 3 by binding to CCAAT enhancer-binding protein beta. In smooth muscle cells (SMCs), MR regulates contraction by inhibiting the expression of microRNA-155 and increasing the expression of L-type calcium channel Cav1.2 and angiotensin type-1 receptor. Moreover, MR activation in SMCs promotes the expression of α5 subunit integrin and aggravates vascular stiffness. On the other hand, MR phosphorylates and activates non-receptor tyrosine kinases c-Src and mitogen-activated protein kinase (MAPK), thereby leading to vascular inflammation, oxidative stress, proliferation and migration of SMCs, and extracellular matrix deposition. In fibroblasts, MR activation promotes proliferation of fibroblasts by activating Ki-RasA and MAPK1/2 signaling as well as increasing cyclin D1 and E2 expression.

MR antagonists have opposite effects on angiogenesis in different models of diseases. Eplerenone, a selective MR antagonist, has shown to promote angiogenesis in rat hindlimb ischemia by improving the proliferation and function of endothelial progenitor cells[71]. However, Zhao *et al.* have reported that treatment with another MR antagonist spironolactone reduces symptoms of choroidal neovascularization (CNV) in patients with age-related macular degeneration (AMD)[72]. Furthermore, in a rodent model of AMD, MR antagonist or specific deletion of MR in ECs has shown to exert anti-angiogenic effects, partially through the upregulation of decorin expression[72]. These experimental results suggest that endothelial MR regulates angiogenesis differentially in different types of vessels and disease models.

3.1.4. Role of endothelial cell MR in obesity and diabetes

Clinical studies have provided evidence to support a link between MR and vascular dysfunction in obese patients[73]. Hwang *et al.* have found that eplerenone improves vascular endothelial function in older adults, especially those with more total body fat and abdominal fat[73]. The previous studies have shown that EC-specific MR knockout does not affect glucose tolerance or inflammation in white adipose tissue but prevents endothelial dysfunction in obese animals[74]. Similarly, EC MR deficiency has shown to improve endothelial dysfunction, vascular stiffness, and cardiac diastolic dysfunction in western diet (WD)-induced obesity and T2DM female mice, without affecting the body composition or insulin sensitivity of mice fed WD[75,76]. Mechanistically, EC MR deletion ameliorates WD-induced aortic fibrosis and stiffness by inhibiting the endothelial expression of sodium channels, oxidative stress, and macrophage polarization, as well as enhancing the endothelial activation of nitric oxide (NO) synthase[76]. These results provide clear evidence that EC MR contributes to endothelial dysfunction and vascular stiffness in obesity and diabetes.

3.1.5. Role of endothelial cell MR in pulmonary arterial hypertension (PAH)

PAH is a syndrome characterized by a progressive increase in pulmonary vascular load and significant pulmonary vascular remodeling[77]. Increased pulmonary artery resistance leads to right ventricle remodeling and failure[77,78]. The previous studies have reported that plasma

aldosterone levels are elevated in animal models and in patients with PAH, implying that MR signaling may be involved in the pathophysiological process of PAH[79-81]. Moreover, treatment with spironolactone or eplerenone attenuates pulmonary vascular remodeling without affecting the structure and function of the right ventricle in animal models of PAH[82,83], suggesting that the main protective role of MR antagonists is related to pulmonary vessels. In a recent study, Kowalski *et al.* corroborated previous observations that MR antagonists alleviate pulmonary arteriole remodeling and right ventricular hypertrophy through a mouse model of hypoxia-induced PAH[84]. Surprisingly, MR deletion in ECs attenuates hypoxia-induced PAH and right ventricular failure, but its deletion in smooth muscle cells (SMCs), fibroblasts, or myeloid cells does not have any significant effect[84]. Meanwhile, EC MR deficiency has shown to inhibit pulmonary arteriole remodeling and right ventricular hypertrophy, thus recapitulating the beneficial effects observed in eplerenone treatment[84]. Mechanistically, MR deletion in ECs attenuates the expression of genes related to blood pressure and Notch signaling pathway regulation in hypoxia-treated primary pulmonary ECs[84]. Of note, MR deficiency inhibits the upregulation of endothelin-converting enzyme 1 and endothelin receptor B, which are both elevated in response to hypoxic stimulation[84]. However, further investigation is needed to determine if the low expression of endothelin-converting enzyme 1 and endothelin receptor B in MR-deficient ECs improves pulmonary vascular remodeling. Moreover, SMCs, fibroblasts, and inflammatory cells are also involved in pulmonary arterial remodeling in PAH. However, only EC MR deletion can improve the PAH phenotype, suggesting the existence of a crosstalk between endothelial and other cell types. More studies are needed to understand the detailed molecular mechanisms.

3.2. Role of MR in SMCs

3.2.1. Role of SMC MR in hypertension

SMCs regulate blood pressure by modulating vasoconstriction[85]. It has been proposed that uncontrolled proliferating SMCs account for media thickening and vascular stiffness in the pathological process of hypertension[85]. The importance of MR in SMCs for blood pressure regulation has been widely reported[24,86,87]. Studies in mouse model have demonstrated that SMC-specific MR deficiency lowers blood pressure in both aged mice and high sodium-induced hypertensive mice[24,86]. Meanwhile, SMC-specific MR knockout mice have shown improved contractile function and anti-oxidative stress response to Ang II[24]. Mechanistically, MR regulates SMC contraction by inhibiting the expression of microRNA-155 and increasing the expression of L-type calcium channel Cav1.2 and angiotensin type-1 receptor[87] (Figure 3). On the other hand, SMC-specific MR deletion ameliorates vascular stiffness in aldosterone/salt-induced hypertensive mouse model with decreased expression of α5-subunit integrin[86] (Figure 3). Lu *et al.* have found that in SMCs, Ang II acts through angiotensin type 1 receptors to phosphorylate and activate the δ isoform of protein kinase C, which in turn activates the transcriptional activity of MR and subsequently promotes the expression of MR target genes as well as the proliferation of SMCs[88].

3.2.2. Role of SMC MR in MI and HF

The role of SMC MR in MI has also been investigated. It has been demonstrated that MR deletion in SMCs improves coronary and left ventricular (LV) dysfunction in mouse MI model[89]. Mechanistically, SMC-specific MR deficiency exerts a protective role in post-MI hearts by improving LV compliance and elastance as well as reducing interstitial fibrosis and oxidative stress[89]. However, the LV ejection fraction, LV mass, and heart infarct sizes have been shown to be similar between SMC MR knockout mice and control mice after MI. MR blockage by finerenone (nonsteroidal MR antagonists) has shown similar effects as well as[89]. These results support that SMC MR contributes to coronary and left LV dysfunction after MI. Recent animal experiments have suggested that SMC MR deletion exerts protective effect on transverse aortic constriction (TAC)-induced HF with markedly improved ejection fraction, cardiac stiffness, ventricular dimensions, intracardiac pressure, pulmonary edema, and exercise capacity[90]. Mechanistically, MR deletion in SMCs protects cardiac function and adverse cardiac remodeling by alleviating cardiomyocyte hypertrophy, inhibiting cardiac interstitial and perivascular fibrosis, reducing myocardial inflammation, as well as increasing cardiac capillary density and coronary blood flow reserve[90].

3.3. Role of MR in fibroblasts

Fibroblasts are the most important source of cardiac extracellular matrix (ECM), and they play an important role in the pathogenesis of MI, hypertension, and HF[91]. It has been reported that MR is expressed in fibroblasts[92]. *In vitro* studies have verified the direct role of MR in cardiac fibroblasts. Stockand and Meszaros have demonstrated that aldosterone is able to stimulate cardiac fibroblast proliferation through the activation of Ki-RasA and mitogen-activated protein kinase (MAPK)1/2 signaling[93] (Figure 3). This conclusion is supported by the findings of another experiment, showing that aldosterone promotes rat cardiac fibroblast proliferation by increasing cyclin D1 and cyclin E2 expression[94] (Figure 3). These findings suggest that aldosterone-induced MR activation promotes cardiac fibroblast proliferation *in vitro*. Whether

aldosterone promotes ECM production through the direct activation of fibroblasts remains a controversy. Fullerton *et al*. have shown that aldosterone has no direct effect on collagen synthesis in cultured rat cardiac fibroblasts[95]. On the contrary, Brilla *et al*. have demonstrated that low concentration of aldosterone increases collagen synthesis in cultured cardiac fibroblasts, and the effect of aldosterone can be inhibited by spironolactone[96]. Previous animal studies have shown that fibroblast-specific MR deficiency has no effect on cardiac function, cardiac hypertrophy, and fibrosis following TAC[97]. It has not been investigated whether fibroblast MR plays a role in other CVDs.

4. Cardiomyocyte MR and CMDs

4.1. Role of cardiomyocyte MR in MI and HF

Cardiomyocyte MR is known to be involved in cardiac remodeling processes following ischemia[98]. Cardiomyocyte-specific MR deficiency exerts a protective role in MI by improving infarct healing and cardiac function[99]. Mechanistically, cardiomyocyte MR deficiency inhibits oxidative stress, reduces cardiomyocyte apoptosis, enhances neovascularization, and prevents ECM deposition and cardiac hypertrophy following MI. At the molecular level, cardiomyocyte MR deletion reduces apoptosis and promotes healing by activating NF-κB signaling in the early stage of MI[99] (Figure 4). Cardiomyocyte MR is also crucial for determining acute cardiac functional recovery after ischemia-reperfusion injury[100]. Cardiomyocyte MR ablation can improve the recovery of cardiac systolic function and reduce arrhythmia post-ischemia/reperfusion[100]. The enhanced systolic function and decreased arrhythmia in the heart of cardiomyocyte MR knockout mice have been found to be associated with decreased calcium/calmodulin-dependent protein kinase II (CaMKII) activation and sodium-hydrogen exchanger-1 expression (NHE-1)[100] (Figure 4). CaMKII is involved in pathophysiological MR signaling in ischemic heart disease[101]. Moreover, the inhibition of NHE-1 could suppress ventricular arrhythmia in an ischemia-reperfusion model[102]. However, the ablation of MR in myocytes does not affect the development of cardiac hypertrophy, fibrosis, apoptosis, or inflammation in TAC mouse model despite its protective effects on cardiac dilation and dysfunction[97].

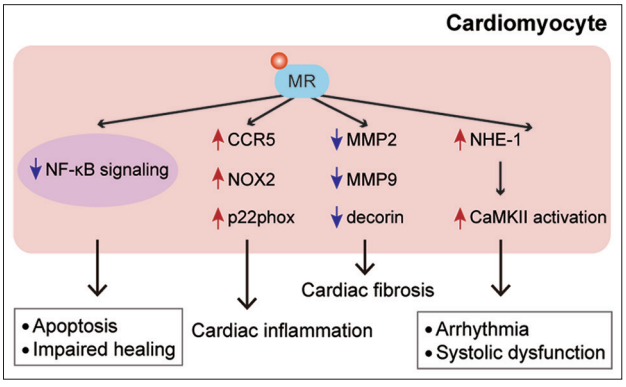

Figure 4. Role of mineralocorticoid receptor (MR) in cardiomyocytes. MR activation in cardiomyocytes affects the heart through different mechanisms. MR activation in cardiomyocytes (i) inhibits the early activation of nuclear factor κB (NF-κB) signaling, which is a key signaling component for early inflammatory activation and healing after myocardial infarction; (ii) promotes cardiac inflammatory responses by increasing the expression of T-cell chemoattractant CCR5, nicotinamide adenine dinucleotide phosphate oxidase subunit NOX2, and p22phox; (iii) enhances cardiac fibrosis by decreasing the expression of decorin and inhibiting matrix metalloproteinase 2/MMP9 activity; (iv) increases the expression of sodium-hydrogen exchanger-1, which in turn activates calcium/calmodulin-dependent protein kinase II, and ultimately leading to arrhythmia and systolic dysfunction.

4.2. Role of cardiomyocyte MR in non-ischemic cardiac injury

In a deoxycorticosterone/salt mouse model, cardiomyocyte MR deletion inhibits inflammatory responses by reducing the expression of T-cell chemoattractant CCR5, nicotinamide adenine dinucleotide phosphate oxidase subunit NOX2, and p22phox in the heart[103] (Figure 4). Moreover, cardiomyocyte-specific MR deficiency inhibits cardiac fibrosis by increasing the expression of decorin and matrix metalloproteinase 2 (MMP2)/MMP9 activity[103] (Figure 4). However, cardiomyocyte MR deletion does not affect cardiac function in this model[103]. On the other hand, cardiomyocyte MR plays an important role in cardiac arrhythmia[104]. Cardiac-specific overexpression of human MR leads to a high rate of sudden death without cardiac structural alteration[104]. The high mortality rate could be prevented by spironolactone[104]. In a study, surviving mice showed severe electrocardiography abnormalities, including prolonged ventricular repolarization and arrhythmias[104]. Mechanistically, cardiac MR overexpression causes ion channel remodeling, leading to an increase in action potential duration and calcium transient amplitude[104]. The role of cardiomyocyte MR in doxorubicin-induced cardiotoxicity has also been investigated[105]. Doxorubicin is widely used in cancer therapy, but its application is limited by cardiotoxicity[105]. The previous data have shown that both eplerenone and cardiomyocyte-specific MR deficiency attenuate doxorubicin-induced LV dysfunction[105]. These data suggest that the beneficial effect of eplerenone is related to the inhibition of cardiomyocyte MR.

5. Role of MR in adipocyte

5.1. Adipocytes

Adipose tissue, also known as "fat," is not only a metabolic organ but an endocrine organ with extraordinary plasticity and heterogeneity. Adipose tissue dysfunction

leads to abnormal responses to physiological signals and contributes to the progression of CMD, along with other pathological consequences. In the last decade, studies have revealed that MR plays an important role in adipose tissue, where MR is involved in regulating the pathophysiological process of adipocytes, including differentiation, autophagy, and adipokine secretion[106]. The regulatory role of MR in white and brown adipocytes is discussed below.

5.2. Function of the MR in white adipocyte

Several studies have demonstrated that MR has an essential role in regulating white adipocyte differentiation and adipogenesis *in vitro*[107-109]. However, Lee *et al.* have provided a contrary perspective that instead of MR, GR plays a dominant role in cortisol-mediated adipogenesis and adipokine production in human adipocytes[110]. Given the different conditions used in these studies, the individual and cooperative roles of MR and GR in regulating adipocyte differentiation require further investigation.

MR expression is increased in the adipose tissue of obese mouse model and obese patients[111,112]. Notably, the metabolic benefits of MR antagonists have been widely demonstrated by several animal studies[40,111,113,114]. MR blockade reverses obesity-induced white adipocyte dysfunction and insulin resistance as well as promotes the browning of white adipose tissue (WAT). Moreover, MR activation is involved in obesity-induced vascular dysfunction. On the contrary, MR blockade by potassium canrenoate improves adipose tissue senescence and vascular dysfunction in obesity[115]. Besides, adipocyte MR overexpression leads to impaired vascular contractility in non-obese mice[116]. Interestingly, a recent human study has shown that eplerenone inhibits interstitial fibrosis in subcutaneous adipose tissue in type 2 diabetes patients[117]. Another recent study has demonstrated that spironolactone ameliorates diet-induced hepatic steatosis and insulin resistance by improving WAT browning and inhibiting hepatic mitochondria dysfunction, oxidative stress, and inflammation[118]. However, the exact role of white adipocyte MR in obesity and its associated metabolic disorders remains uncertain. Several studies using genetic adipocyte-specific MR overexpression or knockout mice have revealed a deteriorative effect of adipocyte MR on the regulation of obesity-related metabolic disorders[112,119,120]. However, two other studies have shown that the depletion of MR in mature adipocytes exerts minor to modest improvements on obesity-associated glucose intolerance, insulin resistance, and hepatic steatosis[121,122]. In addition, another study has observed a relative resistance to diet-induced obesity in transgenic mice overexpressing human MR[123]. The discrepancy between adipocyte MR genetic manipulation and MR antagonists could be attributed to the heterogeneity of adipose tissue. The function of MR in other cell types should be taken into consideration in future work.

5.3. Function of MR in brown adipocyte

Several *in vitro* studies have shown that MR activation reduces the expression of uncoupling protein 1 (UCP-1), which is a thermogenic marker, during brown adipocyte differentiation[124,125]. Finerenone, a nonsteroidal MR antagonist, has been shown to improve the metabolic parameters of high-fat diet-induced obese mice *in vivo* through brown adipose tissue (BAT) activation, without affecting WAT expansion[126,127]. Notably, a recent clinical study has revealed that spironolactone increases human BAT activity in response to cold stimuli and food intake[128]. These studies suggest that brown adipocyte MR plays an important role in the control of energy expenditure in metabolic diseases. Further investigations are needed to determine the exact role of MR in brown adipocyte function and CMD.

6. Role of osteoblast MR in cardiac remodeling

Osteoblasts have endocrine functions and play important roles in homeostatic regulation of the internal environment of the body[129,130]. Osteoblast MR deletion diminishes atrial fibrosis in mutant transforming growth factor beta 1 (TGF-β1) transgenic mice by suppressing osteocalcin (OCN) expression[131]. In cultured atrial fibroblasts, OCN binds to G protein-coupled receptor family C group 6 member A (GPRC6A) and promotes the phosphorylation of protein kinase A (PKA) and cAMP-response element binding protein (CREB), thereby increasing fibroblast proliferation and migration[131]. Osteoblast MR deficiency has shown to improve cardiac function and inhibit adverse cardiac remodeling in a mouse MI model[132]. Mechanistically, calvaria ribonucleic acid (RNA) sequencing data have revealed that MR knockout decreases the expression of OCN, which works through GPRC6A to increase the phosphorylation level of ERK in cultured macrophages, thereby promoting macrophage proliferation and pro-inflammatory phenotypic differentiation[132]. Consistently, MR antagonists have been shown to inhibit the expression and secretion of OCN in post-MI mice and HF patients, which further suggests the existence of MR/OCN axis-mediated communication between osteoblast and the heart in pathological cardiac remodeling[132].

7. MR antagonists and clinical applications

Clinical trials have demonstrated that MR antagonists (MRAs) have beneficial effects in treating CVD[7].

MRAs can be categorized as steroidal and non-steroidal compounds based on their chemical class[133]. Steroidal MRAs include spironolactone and eplerenone, which have similar therapeutic effects but different pharmacological characteristics[7]. Finerenone is a third-generation, non-steroidal MRA with less side effects compared with steroidal compounds[134] (Table 1).

Spironolactone is a first-generation MRA, which has been used clinically for decades. It was originally approved as a diuretic for the treatment of edema, primary aldosteronism, and essential hypertension[135]. Subsequently, extensive studies have shown that spironolactone has significant benefits for severe HF, refractory hypertension, hypokalemia, and ascites secondary to cirrhosis[133]. The Randomized Aldactone Evaluation Study (RALES) trial has proven that spironolactone improves mortality and morbidity in patients with severe HF[136]. This trial further supports the use of spironolactone in HF patients. Spironolactone is a potent and competitive antagonist of MR. However, it also binds to androgen and progesterone receptors, causing endocrinal side effects, such as gynecomastia, impotence, and menstrual irregularities[136]. The major limitation of spironolactone in clinical application is the occurrence of hyperkalemia[137]. A pharmacoepidemiologic study has noted that there is a rapid increase in incidence of hyperkalemia following the online publication of the RALES trial. This is associated with an increase in spironolactone prescriptions for elderly patients with HF[138]. Subsequent clinical studies have suggested that the judicious use of spironolactone and closer patient monitoring could reduce the incidence of hyperkalemia[139,140]. Of note, it has been reported that 54% of hyperkalemia cases are associated with MRA treatments in MI or HF patients[141].

Table 1. Properties and applications of MR antagonists

MRAs	Spironolactone	Eplerenone	Finerenone
Chemical composition	Steroidal compound	Steroidal compound	Non-steroidal compound
Affinity for MR	High[149]	Low[149]	High[149]
Tissue distribution	Kidney>heart[137]	Kidney>heart[137]	Balanced in kidney and heart[137]
Active metabolites	7α-TMS Canrenone[150]	No active metabolites[150]	No active metabolites[150]
Half-life in humans	7α-TMS: 13.8 h Canrenone: 16.5h[150]	4–6 h[137]	2–3 h[150]
Clinical applications	Edema[135] Primary aldosteronism[135] Hypertension[135] HF[132,135]	Hypertension[142,143] HF[142,143]	DKD[147,148] HF with T2DM[146]
Side effects	Gynecomastia[135] Impotence[135] Menstrual irregularities[135] Hyperkalemia[137]	Hyperkalemia[137,150]	Hyperkalemia (significantly lower incidence)[137]

MRAs: Mineralocorticoid receptor antagonists; 7α-TMS: 7α-thiomethyl-spironolactone; HF: Heart failure; DKD: Diabetic kidney disease; T2DM: Type 2 diabetes mellitus; MR: Mineralocorticoid receptor

Eplerenone is a second-generation MRA with fewer side effects than spironolactone and a greater selectivity for MR[7]. However, it has lower affinity for MR than spironolactone, thus requiring a higher dose to achieve the same effect as the latter[135]. The results of Eplerenone Post-Acute **MI** HF Efficacy and Survival Study (EPHESUS) have revealed that eplerenone therapy reduces overall morbidity and mortality among patients with acute MI complicated by LV dysfunction and HF[142]. Similarly, the clinical benefits of eplerenone on mortality and morbidity in patients with systolic HF and mild symptoms have also been demonstrated in other clinical studies[143]. A randomized clinical trial has found that early eplerenone administration (within 3 – 7 days) post-acute MI improves outcomes in patients with LV systolic dysfunction and HF and this benefit is not evident when eplerenone is administered at a later stage (≥7 days)[144]. Furthermore, treatment with eplerenone during the acute phase of MI is safe and well-tolerated[145].

Finerenone is a novel, selective, nonsteroidal MRA, with the higher selectivity for MR than spironolactone and stronger MR-binding affinity compared to eplerenone[134]. Finerenone effectively blocks inflammation, fibrosis, adverse cardiovascular, and renal events mediated by MR overactivation[146]. The phase III Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) clinical trials have shown that finerenone slows the progression of kidney disease and reduces the risk of cardiovascular events and hospitalization for HF[147,148]. Finerenone confers beneficial effects on cardiovascular outcomes in patients with chronic kidney disease and type 2 diabetes and is well-tolerated in these patients[147,148]. The MR Antagonist Tolerability Study- HF (ARTS-HF) study has shown that finerenone is well-tolerated and decreases the levels of N-terminal (NT)-pro hormone B-type natriuretic peptide (NT-proBNP) to a similar extent compared with eplerenone in patients with worsening HF with reduced ejection fraction and chronic kidney disease and/or diabetes mellitus, thus suggesting the beneficial effects of finerenone[146]. The effects of finerenone in other CMD

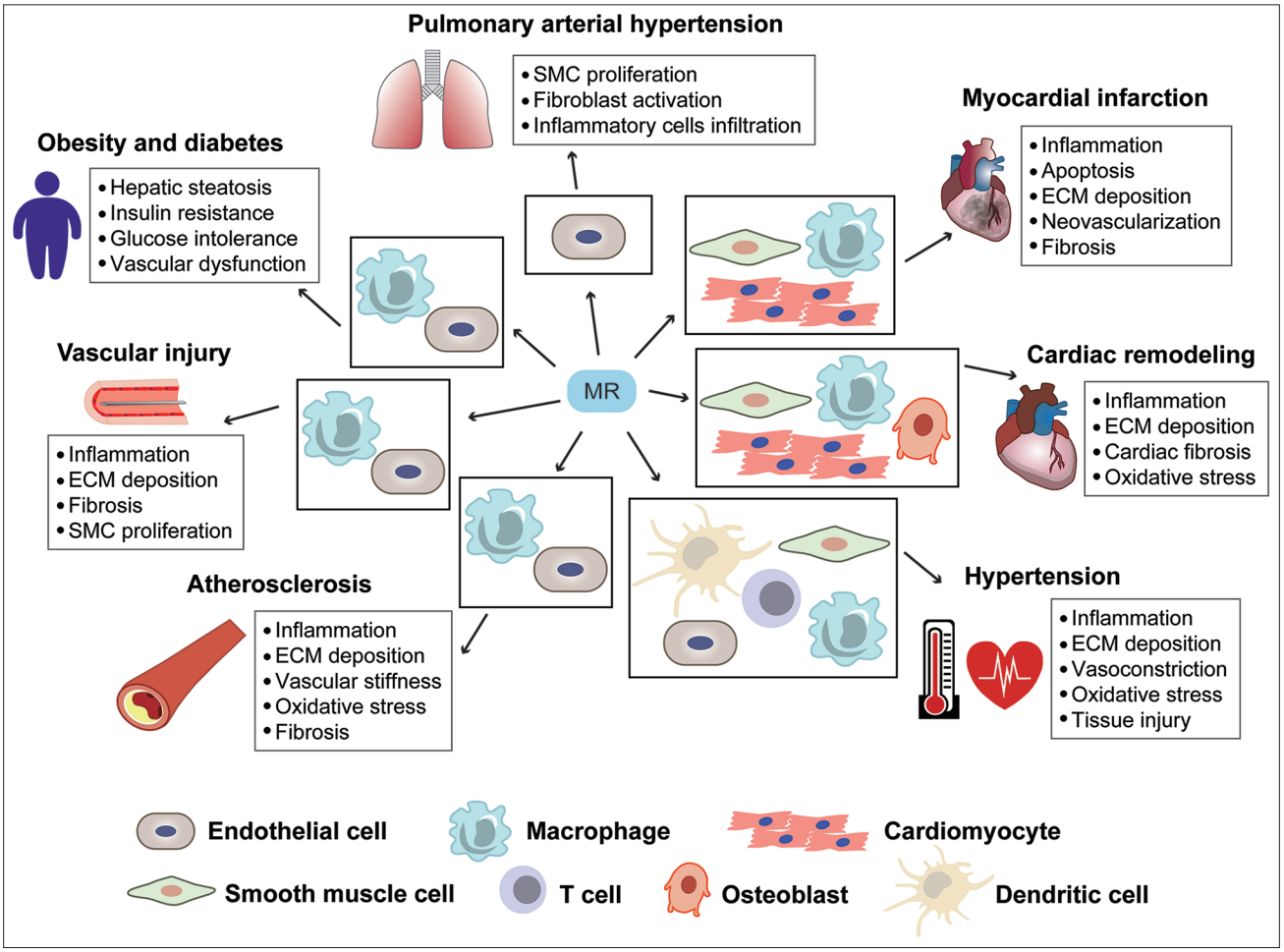

Figure 5. Role of mineralocorticoid receptor (MR) in the pathogenesis of cardiometabolic diseases. MR is expressed in a variety of cells and contributes to the pathological processes of cardiometabolic diseases. ECM: Extracellular matrix; SMC: Smooth muscle cell.

conditions such as hypertension, MI, and atherosclerosis, require further investigations.

8. Conclusions and perspectives

MR has been studied for more than 30 years, and substantial progress has been made in the understanding of the role of MR in CMDs. MR is expressed in almost all tissues and organs involved in cardiovascular homeostasis and participates in the pathophysiological process of CMDs (Figure 5). Inhibiting the functional activity of MR in these tissues may improve CMD outcomes. Although many animal experiments and clinical trials have described the function and role of MR in different tissues as comprehensively as possible, MR will continue to be an interesting and important research topic in CMDs, as many questions remain to be answered. The role of MR in some important tissues and cells has not been fully elucidated. For example, it is still not known whether B-cell MR plays a key role in the pathology of CMDs. The role of MR in adipose tissue has also not been fully explored. Elucidating the role of MR in these tissues will help to paint a more complete picture of the function of MR and will likely provide a more comprehensive basis for new therapeutic strategies.

MRAs, including steroidal and non-steroidal classes, are commonly used to treat CVDs in clinical practice. The novel non-steroidal MRA, finerenone, has a lower risk of hyperkalemia than steroidal MRAs due to differences in tissue distribution, receptor inactivation, drug half-life, and other factors. Recently, an increasing number of evidence has shown that finerenone could significantly improve renal prognosis and reduce the risk of CVD in adult patients with chronic kidney disease and T2DM. However, it still lacks direct evidence to support the application of finerenone in the treatment of CVDs, such as HF, MI, atherosclerosis, and hypertension. Illuminating the beneficial effects (and possibly side effects) of finerenone in CMDs will facilitate a broader application of this drug in clinical practice and inspire the development of the next generations of MRAs.

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Conflict of interest

The authors declare that they have no competing interest.

Author contributions

Conceptualization: Jian-Yong Sun, Yong-Li Wang, Hong Zhu, Sheng-Zhong Duan

Writing – original draft: Jian-Yong Sun, Yong-Li Wang, Hong Zhu

Writing – review & editing: Jian-Yong Sun, Sheng-Zhong Duan.

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