Mineralocorticoid receptor activation and antagonism in cardiovascular disease: cellular and molecular mechanisms

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Aldosterone controls salt–water homeostasis by acting on the mineralocorticoid receptor (MR), a ligand-activated transcription factor, in kidney epithelial cells. However, it is now evident that the MR is expressed in multiple cell types and tissues, acting as a key driver of cardiovascular disease. MR antagonists have proven to be highly efficient in patients with heart failure and reduced ejection fraction, and they are a cornerstone of contemporary therapy. In the past decade, a series of experimental studies using models with cell type–specific MRs uncovered the cellular and molecular mechanisms underlying its detrimental effect on left ventricular remodeling. Based on these findings, the potential of MR antagonists has been evaluated in other cardiovascular diseases, including coronary artery disease, arterial hypertension, heart failure with preserved ejection fraction, pulmonary hypertension, atrial fibrillation, and heart valve disease. The present review summarizes the current knowledge on MR activation and antagonism in cardiovascular disease.

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Aldosterone, a steroid hormone produced by zona glomerulosa cells of the adrenal cortex, is a central effector hormone of the renin–angiotensin–aldosterone system.[1,2] The physiological role of aldosterone is to control salt–water homeostasis by acting on the mineralocorticoid receptor (MR), a ligand-activated transcription factor, in kidney epithelial cells. Aldosterone via the MR leads to an upregulation and activation of the amiloride-sensitive epithelial Na^+ channel, thereby increasing Na^+ reabsorption and K^+ secretion.[2] The first MR antagonist (MRA), spironolactone, was developed as an antihypertensive drug, with the intention to prevent Na^+ retention and decrease blood volume.[3,4] However, because of its activity at the progesterone receptor and other nuclear receptors, spironolactone may cause relevant side effects, such as gynecomastia.[3] This effect could be ameliorated by the second-generation compound eplerenone and, more recently, a new class of highly selective, potent nonsteroidal MRAs. such as finerenone and esaxerenone.[3,4]

The protective cardiovascular effect of MRAs was first attributed to their effects on diuresis, blood volume, and electrolyte homeostasis.[5] However, the MR is expressed in multiple cell types and tissues outside the kidney, and it is now evident that MR in extrarenal tissues is a key driver of disease (Figure 1).[6,7] More than 20 years ago, major clinical trials provided evidence that MRA treatment improves mortality and morbidity in patients with heart failure with reduced ejection fraction (HFrEF), leading to a class IA guideline recommendation.[8–10] Since then, a series of experimental studies uncovered the cellular and molecular mechanisms underlying the beneficial effect on left ventricular (LV) remodeling. Based on these findings, the potential of MRAs has been evaluated in other cardiovascular diseases, including coronary artery disease, arterial hypertension, heart failure with preserved ejection fraction (HFpEF), pulmonary hypertension (PH), and heart valve disease. The present review summarizes the current knowledge on MR activation and antagonism in cardiovascular disease.

HFrEF and post–myocardial infarction remodeling

MRAs are established drugs in the treatment of chronic HFrEF, as evidenced in multiple studies.[8] The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart

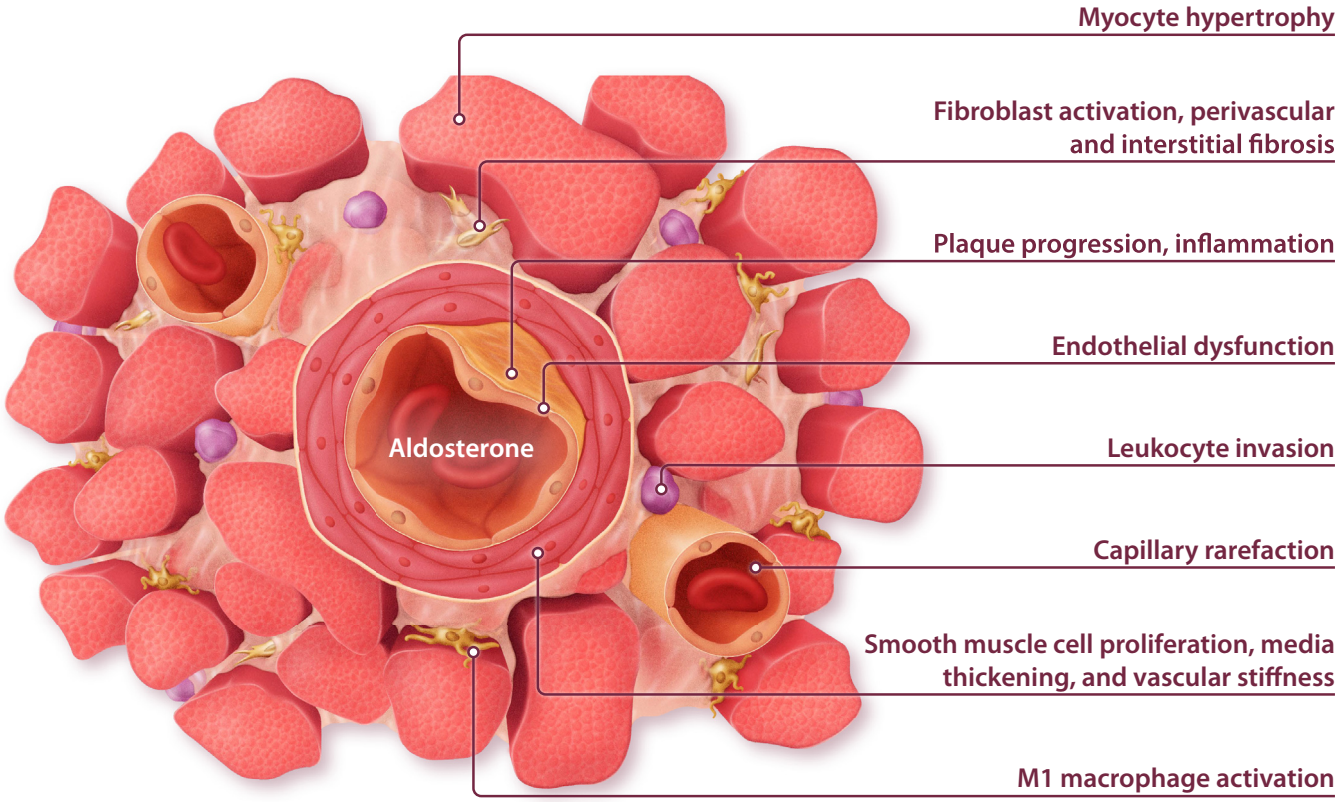

Figure 1 | Biological effects of mineralocorticoid receptor activation in the cardiovascular system.

Failure (EMPHASIS-HF) demonstrated a reduction in mortality by 24% in patients with HFrEF and mild symptoms treated with eplerenone versus placebo.[11] In the Randomized Aldactone Evaluation Study (RALES), spironolactone had a similar effect in patients with severe heart failure symptoms, in whom mortality was reduced by 30% versus placebo.[12] Studies have shown that, like spironolactone and eplerenone, the nonsteroidal MRA finerenone reduced levels of pro-B-type natriuretic peptide (BNP) or N-terminal BNP (NT-proBNP) in phase II trials.[13,14] Early initiation of MRA treatment in patients with acute heart failure was found to be safe and well tolerated.[15,16] Eplerenone improved outcomes of patients with impaired LV function after myocardial infarction (MI).[17] Subsequent studies tested the hypothesis that initiation of MR blockade early after MI might prevent cardiac remodeling and the occurrence of heart failure. When initiated within 72 hours after symptom onset, MRA treatment improved BNP/NT-proBNP levels in patients without preexisting heart failure.[18] However, in a later study, a potential benefit of early MRA treatment on clinical outcomes was observed only in the subgroup of high-risk patients with ST-elevation MI.[19] An individual patient-level meta-analysis of 3 large randomized controlled trials in patients with HFrEF also demonstrated a 23% reduction in sudden cardiac death with MRA treatment.[20] In patients with newly diagnosed HFrEF, treatment with higher MRA dosages was associated with superior amelioration of LV ejection fraction beyond 3 months.[21]

Experimental studies using MRAs in animal models of heart failure and post-MI remodeling demonstrated beneficial effects on cardiac hypertrophy, fibrosis, or both (Figure 1).[22–25] Subsequently, the use of mouse models with cell-specific MR deletion provided evidence that these effects were mediated by MR activation in cardiovascular cells. MR deletion from cardiac myocytes resulted in smaller scar size, less fibrosis of the remote tissue, and improved LV function.[26] Reduced fibrosis after ischemic injury was associated with attenuated oxidative stress and myocyte apoptosis, but higher numbers of neutrophils and monocytes were detected in myocardial tissue from MR-deficient mice compared with wild-type mice.[26] Notably, MR deletion from myeloid cells likewise improved LV remodeling and induced a shift toward the more-reparative M2 macrophage subtype.[27] MR deletion from smooth muscle cells (SMCs) attenuated LV fibrosis but had minor effects on LV function.[25] This implies that MRAs have effects on different cell types that synergistically contribute to damage control and healing after MI.

The centrality of inflammation in mediating the deleterious effect of MR activation has been confirmed in models of chronic heart failure (Figure 2).[25–54] MR deletion from myeloid cells prevented cardiac remodeling in response to pressure overload or N(G)-nitro-L-arginine methyl ester

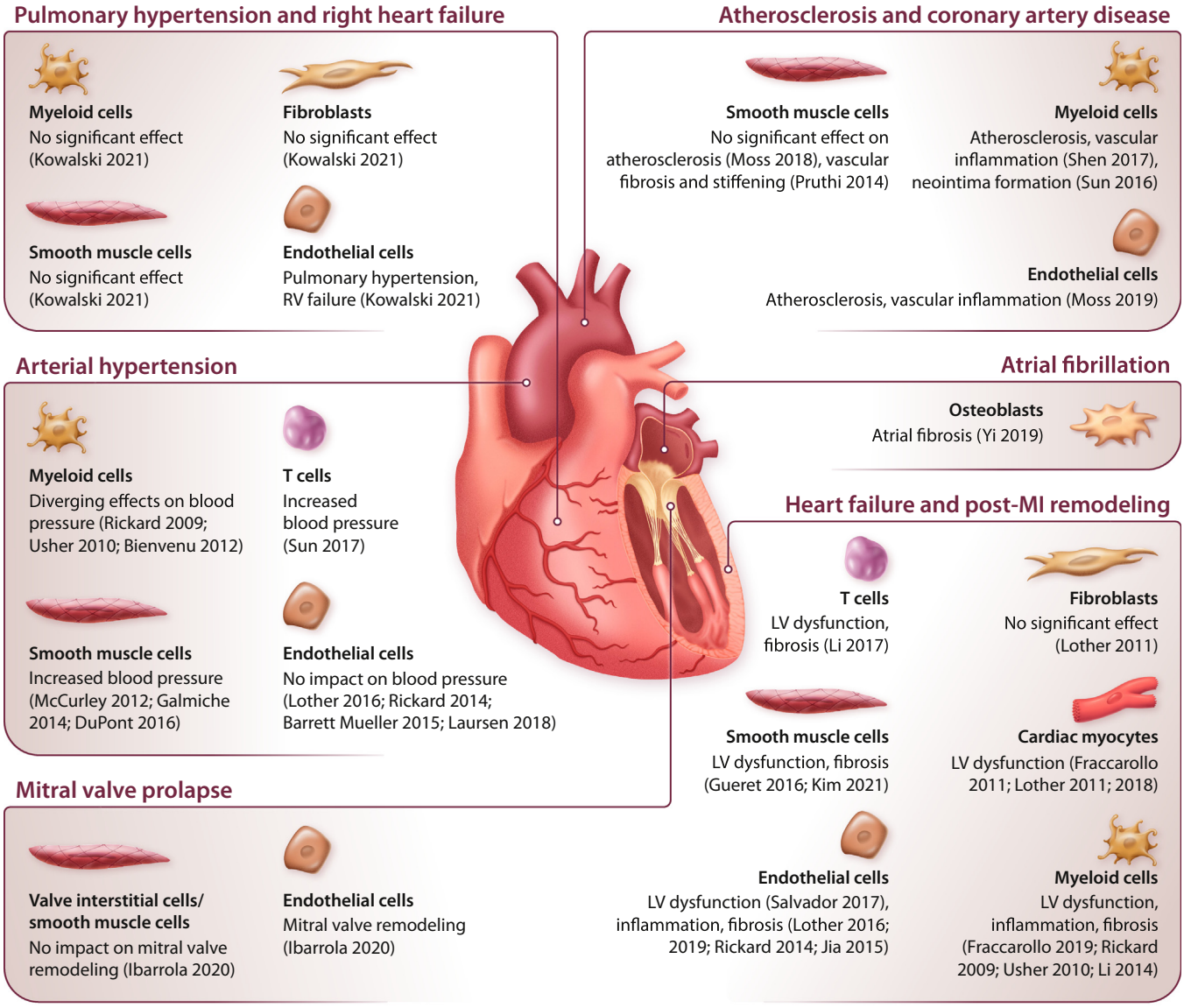

Figure 2 | Cell type–specific function of the mineralocorticoid receptor (MR) in cardiovascular disease.[25–54] Function of the MR in different cardiovascular cell types and diseases as revealed by experimental studies using mouse models with cell type-specific MR deletion. LV, left ventricular; MI, myocardial infarction; MR, mineralocorticoid receptor; RV, right ventricular.

(L-NAME)/angiotensin II infusion.[28,29] Similar effects were observed in mice lacking MRs in T cells.[30] Very recently, SMC MR deletion was shown to improve pressure overload–induced LV hypertrophy, inflammation, fibrosis, and dysfunction.[31] MR deletion from endothelial cells or cardiac myocytes improved LV function, but in contrast to ischemic injury, it did not regulate fibrosis after pressure overload.[32,33] No differences were detected after MR deletion from fibroblasts.[32] These findings suggest that the impact of the MR on cardiac remodeling depends on not only the cell type but also the type of injury.

Substantial efforts have been made to decipher molecular regulatory mechanisms behind aldosterone/MR-induced LV remodeling. Well-characterized inflammatory and fibrotic effector molecules of the MR in the cardiovascular system include galectin 3 (LGALS3) and lipocalin 2 (NGAL).[55–58] Intriguingly, pharmacologic inhibition by modified citrus pectin or genetic deletion of galectin 3 attenuated aldosterone-induced cardiac remodeling.[55,56] Plasma levels of NGAL were positively correlated with circulating aldosterone levels and fibrosis biomarkers in humans.[57] Deletion of NGAL from immune cells prevented LV fibrosis in response to aldosterone infusion.[58] Likewise, MR deletion from myeloid cells improved cardiac remodeling after myocardial infarction, which was associated with reduced NGAL expression in cardiac macrophages.[27] A recent high-throughput screening of microRNAs identified miR-181a as a crucial regulator of MR signaling.[59] miR-181a overexpression downregulated NGAL expression *in vitro* and *in vivo* and improved cardiac function in a rodent MI model.[59]

HFpEF

The prevalence of HFpEF is increasing and already accounts for more than 50% of heart failure cases.[60] Despite overlapping symptoms, HFpEF is considered to be a separate entity from HFrEF.[60] Compared with patients with HFrEF, patients with HFpEF are older, more often female and obese, and have more comorbidities, such as diabetes and kidney disease, that are associated with chronic inflammation.[60,61] MR activation increases oxidative stress and impairs nitric oxide (NO) signaling, leading to endothelial dysfunction, inflammation, and perivascular fibrosis.[34] Although the ideal preclinical model to study HFpEF remains to be defined, a clear finding is that MR activation is associated with many of the pathophysiological features that characterize HFpEF.[62,63] MRAs improved diastolic dysfunction induced by obesity, ovariectomy, nephrectomy, or deoxycorticosterone acetate (DOCA)/salt hypertension in mice.[64–67] Cell type–specific MR deletion from cardiac myocytes attenuated leukocyte invasion and fibrosis after DOCA treatment.[68] In line with the paradigm of systemic inflammation in HFpEF, MR deletion from endothelial cells or myeloid cells demonstrated the most striking effect on cardiac remodeling (Figure 2).[35–38,54,69]

Early clinical trials suggested beneficial effects of MRAs in patients with HFpEF.[70–72] Thus, it was unexpected that spironolactone failed to improve the composite primary outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure in the large phase III Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial.[73] However, serious concerns about study conduct call into question the validity of the study.[74,75] In the FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease (FIGARO-DKD) trial, the non-steroidal MRA finerenone reduced the incidence of cardiovascular events in patients with diabetic kidney disease,[76] a patient group at high risk for developing HFpEF.[60] Notably, the beneficial effect of finerenone was predominantly driven by a lower rate of hospitalization for heart failure, although patients with preexisting HFrEF were excluded from the trial.[76] Two additional phase III clinical trials comparing spironolactone (Spironolactone in the Treatment of Heart Failure [SPIRIT-HF]; NCT04727073; EudraCT 2017-000697-11) and finerenone (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure [FINEARTS-HF]; NCT04435626) with placebo in patients with heart failure and mid-range or preserved ejection fraction are currently ongoing.

In the Heart 'OMics' in AGEing (HOMAGE) trial, spironolactone reduced synthesis and increased degradation of type I collagen, and reduced blood pressure, left atrial volume, and BNP levels in people at risk for HFpEF.[77] Whether early MRA treatment is able to delay occurrence of heart failure in such populations remains to be determined.

Atherosclerosis and coronary artery disease

Atherosclerosis and coronary artery disease are considered chronic inflammatory diseases,[78] and the strong influence of MR on vascular inflammation described above suggests a role for the MR in their pathophysiology. In the apolipoprotein E knockout mouse model, aldosterone infusion exacerbated atherosclerosis development.[79] Conversely, MRAs attenuated inflammation and formation of reactive oxygen species but improved NO bioavailability and vascular function in obesity models.[80–83] Aldosterone effects on monocyte recruitment and plaque inflammation were attenuated in mice lacking placental growth factor[79] or intercellular adhesion molecule 1,[84] indicating an interaction of endothelial cells and monocytes in the process. *In vitro*, MR promoted the expression of inflammatory molecules in endothelial cells and SMCs.[39,54,85–87] *In vivo*, MR deletion from endothelial cells or myeloid cells, but not from SMCs, ameliorated vascular inflammation in mouse models of atherosclerosis.[39–41] In addition, stimulation of monocytes with aldosterone augmented inflammatory cytokine production, depending on an upregulation of the fatty acid synthesis pathway.[88] The growing body of literature on the function of myeloid cell MRs in innate immunity and atherosclerosis has been summarized by van der Heijden *et al.* (2018).[89] Aside from their effects in atherosclerosis, MRA treatment and MR deletion from SMC or myeloid cells yielded beneficial effects on vascular remodeling following mechanical injury,[42,43,90] indicating a potential benefit of MRAs on postangioplasty restenosis. Despite this compelling experimental evidence, data from clinical trials on MRAs in atherosclerosis are still scarce.[91] The recent Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial showed for the first time that treatment with the novel MRA finerenone could reduce the incidence of MI in patients with diabetic kidney disease,[92] indicating a potential role of MRAs in the primary prevention of cardiovascular events.

Arterial hypertension

The impact of aldosterone and MR on arterial hypertension has been recognized for decades. For instance, aldosterone infusion substantially increases blood pressure in uninephrectomized rats receiving a high-salt diet.[93,94] In addition to its effects on Na^+ and fluid retention, aldosterone controls blood pressure via the MR in cells outside the kidney.[95] Endothelial MR activation induced the production of reactive oxygen species and impaired endothelium-dependent vascular relaxation.[44,80] Notably, these effects were more pronounced in female mice, compared with male mice.[96] MR overexpression led to a moderate increase in blood pressure.[97] However, MR deletion from endothelial cells did not alter blood pressure at baseline or in response to stimulus,[36,44,45,69] indicating that the MR in endothelial cells at physiological expression levels is dispensable for blood pressure control. In contrast, numerous studies point at MRs in SMCs as a key determinant of vascular stiffness and hypertension, particularly in aged mice (Figure 2).[46–48,98] It was suggested that the MR via repression of miR-155 enhances the expression and activity of L-type Ca^{2+} channels in SMCs, leading to an

increase in vascular tone.[46,47] Angiotensin II-induced hypertension and subsequent organ injury were markedly suppressed by MR deletion from T cells.[49] Regarding the role of MR in myeloid cells, partly contradictory results have been reported on the blood pressure response to DOCA/salt hypertension[37] or angiotensin II/L-NAME.[29,38] Spironolactone proved effective in patients with resistant hypertension in multiple clinical trials and is now recommended in patients with sustained hypertension despite triple therapy.[99,100] The nonsteroidal MRA esaxerenone had effectiveness similar to that of eplerenone in lowering blood pressure and is now approved in Japan for the treatment of essential hypertension.[101,102] In a recent phase 2b trial, the nonsteroidal MRA KBP-5074 was able to significantly lower blood pressure in patients with chronic kidney disease and uncontrolled hypertension despite treatment including a renin–angiotensin system inhibitor.[103] In contrast, in patients with chronic kidney disease and well controlled hypertension, finerenone had only minor additional effects on blood pressure.[76,104]

PH and right heart failure

Increased plasma aldosterone levels have been observed in patients with PH and in mice after exposure to chronic hypoxia,[50,105,106] hinting at a role for the MR in pulmonary vascular remodeling. In fact, aldosterone stimulation induces PH phenotypes *in vivo* and in cultured SMCs or endothelial cells *in vitro*.[50,107–109] MRAs improve vascular remodeling and right ventricular function induced by chronic hypoxia or monocrotaline in mice and rats.[50,107,110] However, MRA treatment had no effect in a pulmonary artery banding model, implying that the benefit of MRAs on right ventricular function can be indirectly explained by the reduced afterload.[110] Experimental studies using mice with cell type–specific MR deletion revealed that the detrimental effect of aldosterone on the pulmonary vasculature is mediated by the MR in endothelial cells rather than SMCs, fibroblasts, or macrophages (Figure 2).[50] Gene expression analyses and *in vitro* studies point at an interaction between endothelial cells and other cell types in the process, involving the endothelin-1 signaling pathway and paracrine crosstalk via exosomes.[50,108,109,111] A *post hoc* analysis from the Ambrisentan for the Treatment of Pulmonary Arterial Hypertension (ARIES) 1 and 2 trials suggested a beneficial effect of spironolactone when added to the endothelin-1 receptor antagonist ambrisentan in patients with PH.[112] A prospective randomized phase 2 clinical trial on MRA use in PH is currently ongoing (NCT01712620).

Potential future directions

Knowledge of MR effects in cardiovascular disease continues to expand, pointing to new potential indications for MRAs. The availability of new, nonsteroidal MRAs may further broaden the spectrum of indications and enable clinical use of MRAs in high-risk patient populations.[4] Preclinical and early clinical data suggest that MRAs may be effective in preventing chemotherapy-induced cardiotoxicity, a relevant side effect of anticancer drugs leading to LV failure, in female patients.[51,113,114] Additionally, growing evidence indicates that MR activation causes adverse remodeling of not only the ventricles, but also the atria. Patients with primary aldosteronism are at higher risk of developing atrial fibrillation compared with patients with essential hypertension.[115] Intriguingly, atrial fibrosis induced by transforming growth factor β was attenuated by MR deletion in osteoblasts (Figure 2).[52] In various experimental models, MRAs reduced atrial fibrosis and thus the burden of atrial arrhythmia,[116–118] suggesting a potential benefit of MRAs in patients with atrial fibrillation. In line with this possibility, a meta-analysis of clinical trials revealed a substantial reduction in the occurrence of atrial fibrillation in MRA-treated patients, compared with control groups.[119]

Mitral regurgitation is a common heart valve disorder often associated with structural deterioration and a disturbed extracellular matrix of the mitral valve leaflets.[120] Recent evidence suggests that aldosterone, by activating the MR, drives proteoglycan production by interstitial cells and endothelial-to-mesenchymal transition in mitral valves.[53] In mice, MRA treatment or MR deletion in endothelial cells attenuated mitral valve remodeling.[53] This effect was accompanied by decreased expression of fibrotic markers in LV tissue in mice treated with spironolactone.[121] Although currently limited to interventional or surgical repair, MRAs may thus represent a new treatment option for mitral regurgitation.[6,120]

Conclusions

Evidence is accumulating from a number of experimental studies demonstrating that MRs in cardiac myocytes, endothelial cells, SMCs, myeloid cells, T cells, and osteoblasts have direct impact on heart failure and other cardiovascular diseases. Depending on the type of disease or stimulus, different cell types have MRs with distinct functions that contribute to the net effect of inflammation and fibrosis following activation. The available insights discussed in this review will provide the basis for further development and the evaluation of classical and novel MRAs for additional cardiovascular indications.

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