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Aldosterone/Mineralocorticoid Receptor Downstream Targets as Novel Therapeutic Targets to Prevent Cardiovascular Remodeling

Jaime Ibarrola, Frederic Jaisser and Natalia López-Andrés

Abstract

The incidence of heart failure (HF) is increasing because of aging of the population. Despite optimal therapy, patients with HF experience disease progression associated with high mortality rates. HF is still the first cause of hospital admission in subjects aged >65 years. The obvious solution for HF epidemics is to prevent new-onset HF with therapies directed specifically to mechanistic targets that are involved in the transition to HF. The mineralocorticoid receptor (MR) and its natural ligand, the hormone aldosterone (Aldo), play important roles during cardiac and arterial remodeling, but the underlying effects are still not understood. MR antagonists are highly recommended for treatment of systolic symptomatic HF. However, adverse effects limit their use in clinical practice. Galectin-3 (Gal-3), neutrophil gelatinase-associated lipocalin (NGAL), and cardiotrophin-1 (CT-1) have been identified as highly focused targets controlling downstream key MR-mediated HF mechanisms. Therefore, interfering with mechanistic pathways involved in downstream MR activation may provide therapeutic alternatives to MR antagonists. The aim of this review is to focus on the role of the MR biotargets in cardiovascular remodeling.

Keywords: biotarget, galectin-3, neutrophil gelatinase-associated lipocalin, cardiotrophin-1

1. Introduction

Inappropriate mineralocorticoid signaling has been shown to play an important role in the progression of cardiovascular disease. Aldosterone (Aldo) is a main regulator of renal sodium reabsorption with an overall effect on volemia and blood pressure. Aldo binds to the mineralocorticoid receptor (MR), which works as a transcription factor of the nuclear receptor family present in the kidney and also in various other non-epithelial cells including the heart and the vasculature [1]. Indeed, new extrarenal pathophysiological effects of this hormone have been characterized, extending its actions to the cardiovascular system [2]. A growing body of clinical and preclinical evidence suggests that Aldo and MR play an important

pathophysiological role in cardiovascular remodeling by promoting changes involving cardiac hypertrophy, fibrosis, arterial stiffness, as well as in inflammation and oxidative stress [3]. In line with these findings, inappropriate MR activation has been shown to promote cardiovascular remodeling in experimental models [4]. The RALES, EPHESUS, and the EMPHASIS-HF clinical trials demonstrated that the addition of MR antagonists (MRAs) to standard care markedly reduced the overall and cardiovascular mortality in patients with systolic heart failure (HF) [5–7]. The beneficial effects were mainly associated with a reduction of cardiovascular fibrosis, as assessed by circulating biomarkers of cardiovascular extracellular matrix [8]. Moreover, results of the recently completed REMINDER (impact of eplerenone on CV outcomes in patients post myocardial infarction, clinical trial number NCT01176968) trial and TOPCAT (NCT00094302) trial suggest that MR blockade might be clinically beneficial, respectively, for acute myocardial infarction healing and progression of HF with preserved ejection fraction.

The molecular targets involved in the remodeling processes modulated by Aldo/MR activation in the cardiovascular system need to be more precisely analyzed. Inflammatory processes are tightly linked with fibrosis during cardiovascular remodeling. In addition to profibrotic targets, there is evidence that Aldo/MR may trigger inflammatory processes negatively impacting on cardiovascular remodeling processes. Thus, MR activation and inhibition modulate the expression of several pro-inflammatory molecules that may contribute to the pathogenesis of cardiovascular remodeling: Aldo/MR activation increases monocyte chemoattractant protein-1 (CCL-2), transforming growth factor- β 1 (TGF- β 1), connective tissue growth factor (CTGF), plasminogen activator inhibitor type-1 (PAI-1), as well as collagen and metalloproteases through MR-dependent mechanisms. The identification of the Aldo/MR-modulated targets in cardiovascular remodeling associated with HF development is actually a medical need. Their inhibition could add therapeutic benefits in patients at high risk for the development of HF and cardiovascular remodeling. In the last years, new candidates to be Aldo/MR biotargets emerged in preclinical and clinical studies, such as galectin-3 (Gal-3), neutrophil gelatinase-associated lipocalin (NGAL), and cardiotrophin-1 (CT-1) (**Figure 1**).

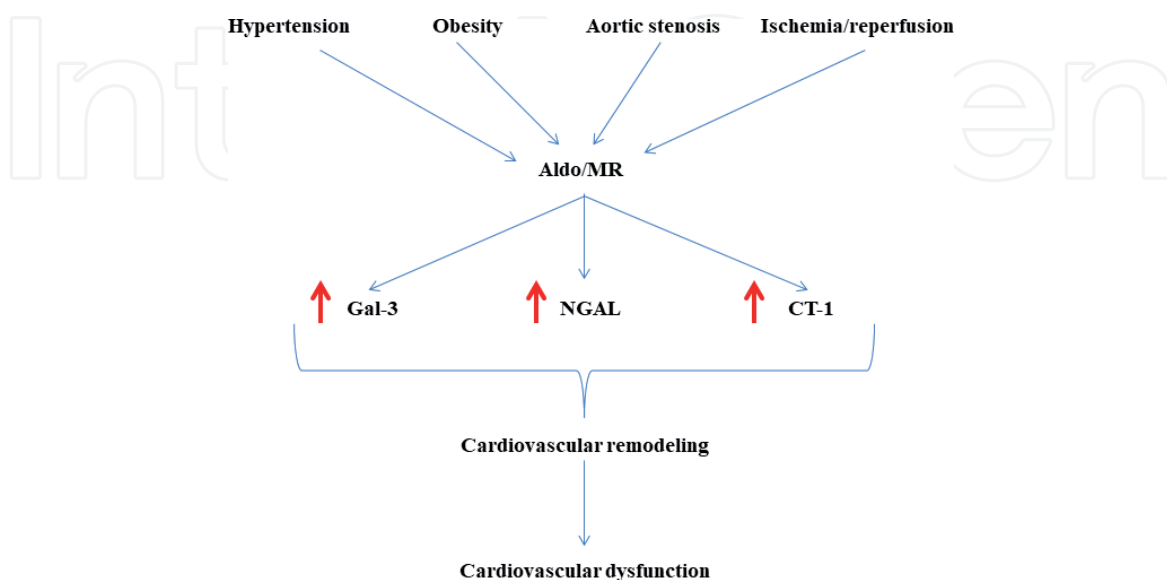


Figure 1. Aldo/MR biotargets Gal-3, NGAL, and CT-1 contribute to cardiovascular remodeling and dysfunction in various pathological and clinical conditions.

2. Galectin-3

2.1 Galectin-3 induces fibrosis, inflammation, and oxidative stress

Galectin-3 (Gal-3) is a 29–35 kDa protein, member of a β -galactoside-binding lectin family, localized in the nucleus, cytoplasm, cell surface, and extracellular space [9]. It is composed of a highly conserved N-terminal domain and a C-terminal carbohydrate recognition domain, which interacts with glycoproteins [10]. The damaging effects of Gal-3 have been associated with its capacity to bind matrix proteins such as cell surface receptors (integrins), collagen, elastin, or fibronectin [11]. The expression of this lectin has been reported in many tissues, including the heart, vessels, and kidney [12]. Moreover, Gal-3 is expressed in many cell types of the cardiovascular system such as cardiac fibroblasts [13], vascular smooth muscle cells [14], endothelial cells [15], and inflammatory cells [16]. Gal-3 is involved in numerous physiological and pathological processes, some of which, inflammation and fibrosis, are pivotal contributing to pathophysiological mechanisms in the development and progression of HF. Indeed, it has been demonstrated in cell culture that Gal-3 turns quiescent fibroblasts into myofibroblasts that produce and secrete matrix proteins, including collagens [13, 17]. Gal-3 exerts its effects during several other stages of fibrogenesis besides collagen production, such as collagen maturation, externalization, and cross-linking, which underscores the pivotal importance of Gal-3 in cardiovascular fibrosis. Moreover, Gal-3 has emerged as a potential mediator of cardiac damage in different pathological situations through its ability to stimulate key pro-inflammatory molecules [16]. Thus, it has been demonstrated that in human cardiac fibroblasts, Gal-3 enhances the production and the secretion of pro-inflammatory and profibrotic mediators such as interleukin (IL)-1 β , IL-6, CCL-2, collagen type I, collagen type III, and fibronectin as well as the activity of MMP-1, MMP-2, and MMP-9 [18]. The *in vitro* findings have been corroborated by animal studies. Thus, Gal-3 administration induces cardiac fibrosis leading to cardiac dysfunction in rats [13]. Additionally, a new line of evidence points out that Gal-3 is involved in reactive oxygen species (ROS) production, although the mechanisms have not been elucidated. Gal-3 increases the expression of Nox4 in cardiac cells and could regulate Nox4-derived ROS levels during cardiac fibrosis [19]. Moreover, Gal-3 downregulates peroxiredoxin-4 inducing a decrease in total antioxidant capacity and a consequent increase in peroxide production and in oxidative stress markers in cardiac fibroblasts [20]. Additionally, Gal-3 downregulates the protective fumarate hydratase increasing fumarate production in human cardiac fibroblasts, leading to increased ROS levels and increased collagen production [21].

2.2 Galectin-3 as a mediator of Aldo/MR activation

Preclinical studies have demonstrated that Gal-3 is a key mediator of cardiovascular and renal fibrosis and dysfunction in pathological conditions associated with high Aldo levels [14, 18, 22–24]. In addition, hyperaldosteronism worsens hypertension-induced cardiovascular fibrosis through an increase of Gal-3 [25]. A summary of Gal-3 mediating Aldo/MR effects is shown in **Figure 2**.

2.2.1 Aldosterone/MR regulates galectin-3 expression *in vitro*

In vitro, in primary cultured vascular smooth muscle cells (VSMCs), Calvier and co-workers described that Aldo increases Gal-3 expression in a dose- and

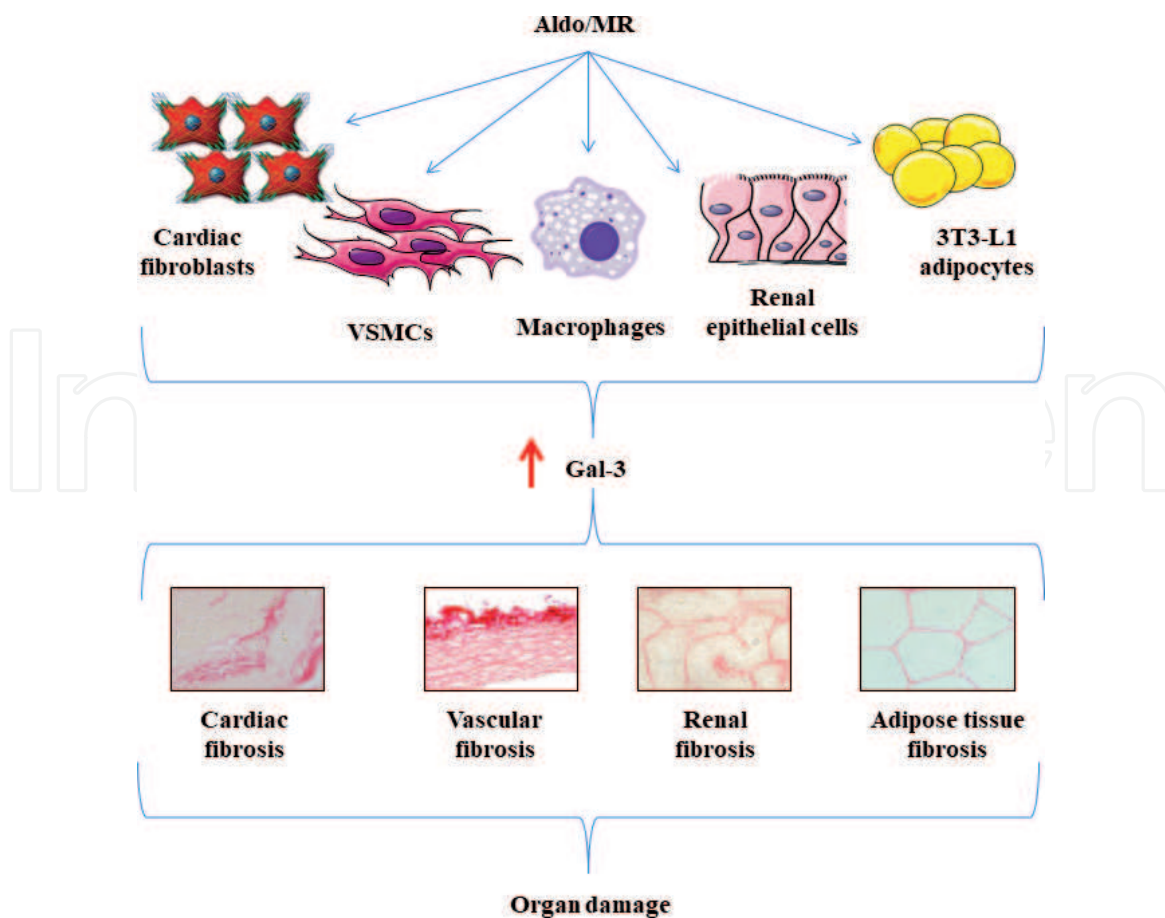


Figure 2.
Gal-3 as a mediator of Aldo/MR effects on fibrosis in several cells and tissues.

time-dependent manner via its MR [14]. Gal-3, via its lectin activity, is a necessary mediator allowing Aldo-induced collagen type I synthesis, because the blockade of Gal-3 with carbohydrates such as modified citrus pectin (MCP, a complex water-soluble indigestible polysaccharide rich in β -galactose) or N-Acetyl-D-lactosamine abolishes Aldo-induced collagen type I deposition. In confirmation of the pharmacological data, Gal-3-depleted VSMCs are resistant to Aldo profibrotic effects, especially collagen type I deposition [14].

In human cardiac fibroblasts, Aldo also increased Gal-3 expression via its MR, and Gal-3 and Aldo enhance pro-inflammatory and profibrotic markers, as well as metalloproteinase activities, those effects being not observed in Gal-3-silenced cells treated with Aldo [18].

In line with these observations, it has been described that Aldo induces Gal-3 secretion in inflammatory cells (macrophage cell lines THP-1 and RAW 264.7 cells) through MR and via PI3K/Akt and NF- κ B transcription signaling pathways [26], amplifying the inflammatory response.

Finally, unpublished data from our group confirmed Gal-3 induction by Aldo via MR in other cell types such and renal cells and 3T3-L1 adipocytes.

2.2.2 Beneficial effects of galectin-3 blockade in experimental models with high aldosterone

In vivo, it has been shown that rats treated with Aldo-salt for 3 weeks present hypertension and display vascular hypertrophy, inflammation, fibrosis, and increased aortic Gal-3 expression. Spironolactone or MCP treatment reverses all the above effects. Interestingly, MCP also blunts Aldo-induced hypertension. In

wild-type (WT) and Gal-3 knockout (KO) mice treated with Aldo for 6 hours or 3 weeks—a normotensive model—Aldo increases aortic Gal-3 expression, inflammation, and collagen type I in WT mice at both the short- and the long-term, whereas no changes occur in Gal-3 KO mice. Altogether, these data show that Gal-3 is required for the inflammatory and fibrotic responses to Aldo in VSMCs in vivo, suggesting a key role for Gal-3 in vascular fibrosis [14]. While using the same experimental models, downstream in vitro experiments in human cardiac fibroblasts and the influence of Gal-3 on Aldo-mediated cardiac and renal effects have been also explored. Hypertensive Aldo-salt-treated rats present cardiac and renal hypertrophy (at morphometric, cellular, and molecular levels) and dysfunction. Cardiac and renal expressions of Gal-3 as well as levels of molecular markers attesting fibrosis are also augmented by Aldo-salt treatment. Spironolactone or MCP treatment reverses all of these effects. In WT mice, Aldo does not alter blood pressure levels but increases cardiac and renal Gal-3 expression, fibrosis, and renal epithelial-mesenchymal transition (i.e., renal epithelial cells differentiate onto extracellular matrix secreting and profibrotic myofibroblasts). Gal-3 KO mice are resistant to Aldo-induced deleterious cardiorenal effects [22].

Aldo levels are increased in spontaneously hypertensive rats (SHR) [27], as well as in hypertensive patients [28], being considered as an inducer of hypertensive organ damage [29]. MR activation and high salt intake cause hypertension as well as inflammation, leading to cardiac inflammation and fibrosis [30]. Gal-3 levels, as well as cardiorenal inflammation and fibrosis, are also increased in the myocardium and kidney from SHR as compared to normotensive controls. Gal-3 pharmacological inhibition using MCP exerts beneficial effects, diminishing cardiorenal inflammation and fibrosis in the absence of blood pressure modifications [18, 23, 31].

Obesity is frequently associated with increased Aldo concentrations in humans [32] and is considered as HF stage A [33]. Obesity upregulates Gal-3 production in the cardiovascular and in the renal system in a normotensive animal model of diet-induced obesity by feeding for 6 weeks a high-fat diet, while Gal-3 inhibition with MCP reduces cardiovascular and renal levels of Gal-3, fibrosis, and inflammation in obese animals without changes in body weight or blood pressure [34]. In adipose tissue, obese male Wistar rats fed with a high-fat diet for 6 weeks present an increase in Gal-3 levels that are accompanied by an increase in pericellular collagen. Obese rats exhibit higher adipose tissue inflammation, as well as enhanced differentiation degree of the adipocytes. Treatment with MCP prevents all the above effects [24]. In summary, Gal-3 emerges as a potential therapeutic target in adipose tissue remodeling associated with obesity—a condition associated with hyperaldosteronemia—and could have an important role in the development of metabolic, cardiovascular, and renal alterations associated with obesity.

In theory, MR activation can promote aortic sclerosis and aortic stenosis (AS), due to its effect on inflammation and fibrosis. Once aortic valve disease has been established, the pressure or volume overload may induce left ventricular dysfunction. In a normotensive animal model of pressure overload (AS), cardiac, vascular, and renal Gal-3 is augmented, and its pharmacological inhibition with MCP prevents cardiovascular and renal functional alterations as well as cardiovascular and renal fibrosis and inflammation [21, 34, 35].

The acute administration of MRAs, either before the onset of ischemia or at the moment of reperfusion, profoundly reduces infarct size (reviewed in [36]). In an animal model of ischemia-reperfusion, cardiac Gal-3 is augmented, and its pharmacological inhibition with MCP prevented cardiac functional, histological, and molecular alterations (unpublished data from our group).

2.2.3 Aldosterone-galectin-3 in clinical populations

As mentioned above, Aldo increases Gal-3 expression in the cardiovascular and renal system as well as in adipose tissue in experimental models.

In a cohort of patients with Aldo-producing adenoma, the authors demonstrated that Gal-3 levels are enhanced. Interestingly, 1 year after adrenalectomy, plasma Gal-3 levels decrease, reinforcing the relation of Aldo-Gal-3 and confirming the results obtained using preclinical models [26]. In contrast with these observations, another group recently described that Gal-3 levels are not increased in patients with primary hyperaldosteronism (as compared to hypertensive patients) and levels do not decrease after adrenalectomy [37].

In untreated congestive HF, Aldo plasma concentrations are elevated in proportion to the severity of the disease and are further increased by the use of diuretic treatment [38]. Interestingly, the serum Gal-3 level has been correlated with serum markers of cardiac extracellular matrix turnover in HF patients, and, therefore, Gal-3 emerges as a biomarker associated with HF onset, morbidity, and mortality [39].

In morbidly obese patients presenting high Aldo levels, insulin resistance, and left ventricular hypertrophy, high Gal-3 levels are associated with a worsening of diastolic function [23]. Moreover, in patients with AS, cardiac Gal-3 is increased and associates with markers of myocardial fibrosis and inflammation [35]. Interestingly, both Aldo and Gal-3 are increased in pulmonary arterial hypertension patients. The axis Aldo/Gal-3 is relevant in pulmonary arterial hypertension because plasma levels of both molecules are associated with pulmonary arterial hypertension severity [40]. Furthermore, Gal-3 positively correlated with Nox4 (related to oxidative stress production) in pulmonary arterial hypertension patients [41].

Given the intimate relation between Aldo, Gal-3, and cardiovascular fibrosis, the predictive value of Gal-3 in patients treated with MRAs has been analyzed. In a cohort of HF patients, MRA treatment does not alter the prognostic value of Gal-3 [42]. An analysis examining the interaction between baseline Gal-3 levels and MRA therapy on outcomes shows no difference in patients who were receiving MRA [43]. Moreover, among patients with chronic HF and elevated Gal-3 concentrations, there is no specific benefit from addition or intensification of MRA therapy [44].

3. NGAL

3.1 NGAL induces fibrosis and inflammation

NGAL, also known as lipocalin-2, 24p3, siderocalin, or uterocalin, is a small glycoprotein of 25 kDa member of the lipocalin family. NGAL is expressed by different cell types including renal, endothelial, VSMCs, macrophages, dendritic cells, cardiomyocytes or cardiac fibroblasts (reviewed in [45]).

NGAL is involved in a wide variety of pathological situations as cardiovascular and renal diseases. Indeed, it has been demonstrated in cell culture that NGAL enhances the production and the secretion of pro-inflammatory and profibrotic mediators such as interleukin (IL)-1 β , IL-6, CCL-2, osteopontin, collagen type I, and collagen type III in human cardiac fibroblasts [46, 47]. NGAL also increases collagen type I production as well as CT-1 and Gal-3 expression and secretion in VSMCs [48]. In cardiac cells, NGAL can also activate the inflammatory pathway NF-kB [47]. Moreover, NGAL treatment induces migration of neutrophils [49], and NGAL KO mice have been shown to present reduced chemotaxis and adhesion

[50]. Moreover, NGAL KO mice subjected to ischemia/reperfusion do not present immune cell recruitment [51].

3.2 NGAL as a mediator of Aldo/MR activation

In vitro, in HL-1 cardiomyocytes, Aldo induces NGAL expression via its MR [52]. These results have been also expanded to other cell types such as cardiac fibroblasts, where Aldo also enhances NGAL expression [47].

Preclinical studies have demonstrated that NGAL is a key mediator of cardiovascular and renal fibrosis, inflammation, and dysfunction in pathological conditions associated with high Aldo levels. Firstly, NGAL has been found to be increased in mice overexpressing MR in cardiomyocytes [52]. Moreover, NGAL KO mice have been found to be resistant to Aldo-salt-induced hypertension and vascular fibrosis [48]. Interestingly, NGAL KO mice subjected to myocardial infarction show lower cardiac fibrosis and inflammation as well as improved cardiac function [47]. Recently it has been described using mice depleted for NGAL in their immune cells by bone marrow transplantation that NGAL from immune cells is mandatory for Aldo-induced cardiac fibrosis and inflammation [53].

In hypertensive patients, NGAL plasma concentrations are elevated and correlate with blood pressure levels [54]. NGAL serum levels are also increased in myocardial infarction patients and in HF patients [55, 56], as well as in obese patients [57]. Importantly, the rise of the complex NGAL/MMP-9 in obese subjects (stage A HF) and its association with plasma Aldo levels suggest that NGAL may serve as a biomarker of MR activation [48].

4. Cardiotrophin-1

4.1 Cardiotrophin-1 induces fibrosis and inflammation

CT-1 is a member of the interleukin-6 superfamily, which is expressed in different tissues including the heart, vessels, skeletal muscle, liver, lung, adipose tissue, and kidney [58, 59]. In the myocardium, CT-1 is produced by both cardiomyocytes and fibroblasts, exerting its action through the glycoprotein 130 (gp130)/leukemia inhibitory factor receptor (LIFR) heterodimer. Whereas CT-1 was initially described as a stress-response factor promoting cardiomyocyte survival [60], chronic exposure to this cytokine induces cardiomyocyte hypertrophy and dysfunction [61, 62]. In addition, experimental in vitro findings in rodent and canine fibroblasts [63–66] as well as in VSMCs [67] suggest that CT-1 behaves also as a profibrotic factor. In particular, CT-1 induces fibroblast growth and proliferation and collagen production. Moreover, in human cardiac fibroblasts, CT-1 has been shown to stimulate myofibroblast differentiation and collagen type I and III production [68]. Coherently, rats chronically exposed to CT-1 present increased fibrosis in the cardiovascular and in the renal system characterized by increased collagen deposition [62]. Finally, data in chronic HF patients indicate that an association exists between CT-1 and collagen type I and III production in the myocardium [68].

4.2 Cardiotrophin-1 as a mediator of Aldo/MR activation

In vitro, in HL-1 cardiomyocytes, Aldo induces CT-1 in a dose- and time-dependent manner via its MR and through the activation of p38MAPK signaling pathway [69]. Moreover, Aldo also enhances CT-1 expression in VSMCs [67]. Interestingly, CT-1 blockade with specific antibodies avoids Aldo-induced hypertrophy of

cardiomyocytes. According to the in vitro data, CT-1-null mice subjected to acute Aldo treatment are resistant to Aldo-induced expression of hypertrophic markers [69]. These results were confirmed in other studies demonstrating that in experimental hyperaldosteronism, the increase of cardiac CT-1 expression is associated with parameters showing left ventricular hypertrophy and fibrosis. Moreover, CT-1-null mice are resistant to Aldo-induced left ventricular hypertrophy and fibrosis [70].

CT-1 expression has been found to be increased in the myocardium of HF patients of different etiologies [68, 71]. Importantly, and according to the results obtained in experimental models, in HF patients high Aldo levels are associated with high CT-1 levels [72].

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