Aldosterone as a modulator of immunity: implications in the organ damage

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High plasmatic levels of aldosterone cause hypertension and contribute to progressive organ damage to the heart, vasculature, and kidneys. Recent studies have demonstrated a role for the immune system in these pathological processes. Aldosterone promotes an inflammatory state characterized by vascular infiltration of immune cells, reactive oxidative stress, and proinflammatory cytokine production. Further, cells of the adaptive immune system, such as T cells, seem to participate in the genesis of mineralocorticoid hormone-induced hypertension. In addition, the observation that aldosterone can promote $CD4^+$ T-cell activation and Th17 polarization suggests that this hormone could contribute to the onset of autoimmunity. Here we discuss recent evidence supporting a significant involvement of the immune system, especially adaptive immunity, in the genesis of hypertension and organ damage induced by primary aldosteronism. In addition, possible new therapeutic approaches consisting of immunomodulator drugs to control exacerbated immune responses triggered by elevated aldosterone concentrations will be described. *J Hypertens* **29:1684–1692 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Abbreviations: Ang II, angiotensin-II; CCR2, chemokine receptor 2; DOCA, deoxycorticosterone acetate; EAE, experimental autoimmune encephalomyelitis; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart and Survival Study; HE, hypertension patients; ICAM-1, intercellular adhesion molecule 1; IGF-IR, insulin-like growth factor-I receptors; LFA-1, lymphocyte function-associated antigen 1; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein 1; NADPHox, NADPH oxidase; NF-κB, nuclear factor-kappaB; OPN, osteopontin; PBMCs, peripheral blood mononuclear cells; RALES, The Randomized Aldactone Evaluation Study; ROS, reactive oxygen species; TGF-ß, transforming growth factor-ß; VSMC, vascular smooth muscle cells

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Introduction

Aldosterone is known as a mineralocorticoid hormone involved in the regulation of electrolyte balance and volume homeostasis [1,2]. By acting on kidney distal nephron, aldosterone promotes sodium reabsorption, water retention, and potassium and magnesium loss, modulating the extracellular space volume and blood pressure [3]. Epithelial cells of the kidney [4] express the mineralocorticoid receptor, a nuclear receptor that after binding to aldosterone translocates to the cell nucleus and modulates expression of specific 'aldosterone-induced' proteins that regulate electrolyte and fluid balance [5]. The role of aldosterone in hypertension and tissue damage was initially demonstrated in patients with adrenal tumors, which showed hypertension, hypokalemia and a metabolic alkalosis due to an excess of aldosterone production [6]. Hypertension caused by aldosterone markedly increases the risk of death from stroke, ischemic heart disease, as well as other vascular disorders. Accordingly, elevated aldosterone levels are considered an independent cardiovascular risk factor [7,8].

During the past few years, studies showing the expression of mineralocorticoid receptor in tissues such as heart [9], blood vessels [10] brain [11], and immune cells [12,13] have extended the view of aldosterone as a steroid hormone acting only on epithelial tissues. Experiments in rats have shown that administration of the nonselective aldosterone blocker spironolactone can prevent vascular damage, despite the persistence of hypertension. These data indicate that aldosterone may act on cardiovascular tissues and contribute to targeting organ damage through nonhemodynamic mechanisms [14]. Accordingly, the renin–angiotensin–aldosterone system is activated in congestive heart failure, leading to an elevation of aldosterone plasma levels that correlates with unfavorable clinical responses [15]. Several studies, such as the Randomized Aldactone Evaluation Study (RALES), the Eplerenone Post-Acute Myocardial Infarction Heart and Survival Study (EPHESUS), and the 4E trials, have shown that mineralocorticoid receptor blockade can significantly improve renal and cardiovascular function in patients suffering from either severe heart failure, acute myocardial infarction or hypertension,

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independently of major alterations in blood pressure or NaCl homeostasis [16–18].

Although the observations described above support the notion that the deleterious effects of mineralocorticoid receptor activation may imply nonhemodynamic effects, the target cells and the relevance of all potential pathways that could be triggered by mineralocorticoid receptor activation to cause end-organ damage are just beginning to be understood. As we will discuss in this review, there is increasing evidence suggesting that some of the effects of aldosterone on the vasculature and target organs, expressed by changes in endothelial function and vascular structure, are mediated by immune cells through a mineralocorticoid receptor-dependent mechanism.

Nonimmunological end-organ damage caused by aldosterone

High plasma levels of aldosterone can induce structural and functional alterations in the heart, kidneys, and blood vessels, such as vascular inflammation, myocardial fibrosis, nephrosclerosis, and tissue remodeling [19–21]. Fibrosis and cardiovascular tissue remodeling can be a consequence of direct actions of aldosterone on fibroblasts and cardiovascular cells. In addition, inflammation could play a causal role in the development of fibrosis. Direct effects of aldosterone over cardiac myocyte were suggested when an excess of aldosterone in a high dietary Na^+ context was observed, which could be associated with cardiac myocyte necrosis [22]. Perivascular fibrosis of intramural coronary vessels and atria caused by chronic administration of aldosterone in uninephrectomized or unilateral renal artery banding rats with preserved cardiac function supported an association between aldosterone and ventricular fibrosis [23,24]. Profibrotic effects of aldosterone have also been demonstrated in humans as a result of myofibroblast growth stimulation and elastin production through activation of insulin-like growth factor-I receptors (IGF-IRs) [25,26]. The effect of aldosterone on the induction of cardiac collagen synthesis was demonstrated by blockade with a low dose of spironolactone, which prevented tissue fibrosis but not the associated hypertension and cardiac hypertrophy [27].

In humans and rodents, aldosterone induces stiffening of resistance arteries and endothelial dysfunction [28,29] that can be prevented by mineralocorticoid receptor antagonists [30]. Activation of the mineralocorticoid receptor by aldosterone regulates the expression of several genes involved in vascular fibrosis, calcification, and inflammatory damage to human vascular smooth muscle cells (VSMCs) [31–34]. More recently, it was shown that VSMCs express intercellular adhesion molecule (ICAM)-1 in response to mineralocorticoid receptor signaling induced by aldosterone, which promotes leukocyte adhesion by specifically associating with lymphocyte function-associated antigen (LFA)-1 expressed on leukocyte surface [35]. Moreover, there is evidence suggesting that aldosterone can be synthesized directly by heart tissue and possibly have local effects through autocrine/paracrine pathways [36,37]. However, this notion remains controversial [38,39].

It has been shown that aldosterone can cause sustained renal damage in rat models of hyperaldosteronism, such as deoxycorticosterone-high salt (DOCA-salt) or the chronic infusion of aldosterone in stroke-prone spontaneously hypertensive rats (SHRSP) drinking 1% NaCl solution. Aldosterone-induced damage is characterized by proteinuria, collagen accumulation, and glomerular structural lesions [40,41]. These deleterious effects of aldosterone on kidney function appear to be due in part to the production of reactive oxygen species (ROS) [42]. The increase in ROS production activates the mitogen-activated protein kinase (MAPK) pathway in renal cortical tissues, which in turn triggers renal injury [42]. In humans, the first study suggesting a role of aldosterone in promoting renal damage reported that patients with glomerular disease treated with angiotensin-converting enzyme (ACE) inhibitors, receiving spironolactone 25 mg daily resulted in a 55% reduction in proteinuria by 4 weeks [43]. Blockade of the multitude of profibrotic and pro-inflammatory effects of aldosterone could affect glomerular hemodynamics and could be beneficial in the long term by reducing progressive renal injury.

Immunological end-organ damage caused by aldosterone

Studies in animal models

Animal studies have provided evidence for the involvement of the innate immune system in the damage associated to high aldosterone levels. The treatment with aldosterone and 1% NaCl added to the drinking water leads to coronary vascular lesions after 4 weeks, characterized by the invasion of monocytes/macrophages and lymphocytes into the intramural coronary arteries [24]. Such an invasion of coronary and systemic vasculature by inflammatory cells takes place before organ injury, suggesting that aldosterone and NaCl could induce an immunostimulatory state [44]. According to this hypothesis, the overexpression of oxidative stress-inducible tyrosine phosphatase and upregulation of enzymes associated with antioxidant defense system in peripheral blood mononuclear cells (PBMCs) could be observed as early as 1 week after aldosterone and NaCl treatment [45]. All these effects were prevented by spironolactone, demonstrating that activation of mineralocorticoid receptor is necessary for the development of aldosterone-induced inflammation. Interestingly, the administration of aldosterone and a high-salt diet to monocyte/macrophage-deficient mice (osteopetrotic, Op/+) showed a dissociation between the effects of aldosterone on oxidative stress and endothelial function, from the effects on vascular stiffness and extracellular matrix content.

Although aldosterone caused stiffening of the arteries of both wild-type and osteopetrotic mice, monocyte/macrophage-deficient mice did not show evidence of oxidative stress and endothelial dysfunction in response to aldosterone, suggesting a direct role of monocyte/macrophage in this process [29].

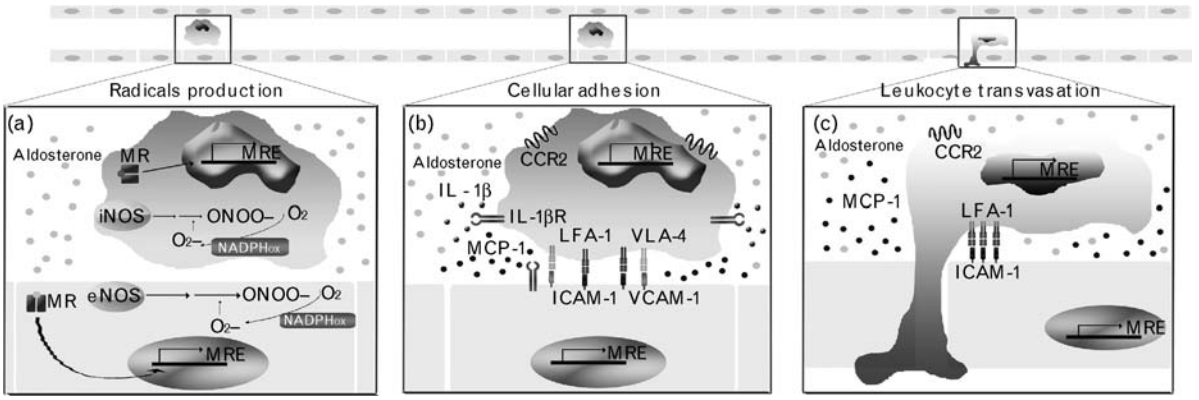
As a result of a rise of aldosterone levels, production of hydrogen peroxide by leukocytes is also increased, which contributes to the lesions on the coronary vascular system. This notion is supported by studies showing that aldosterone and NaCl induce a time-dependent sustained activation of NADPH oxidase (NADPHox) with production of 3-nitrotyrosine and activation of nuclear factor-kappaB (NF-κB) on inflammatory cells [46]. In the kidney, aldosterone upregulates transforming growth factor-β (TGF-β) [47], ED-1 (a macrophage marker), osteopontin (OPN), monocyte chemoattractant protein (MCP)-1, and IL-1β production, as part of fibrotic and inflammatory renal phenotype [48,49] through a mineralocorticoid receptor-dependent mechanism [48]. Whereas MCP-1 plays a role in the recruitment of monocytes to sites of injury by interacting with the chemokine receptor 2 (CCR2) expressed on monocyte surface, IL-1β contributes to increasing the expression of adhesion molecules by immune and endothelial cells through the interaction with IL-1β receptor (IL-1βR). Thus, aldosterone can promote the recruitment and activation of immune cells by several mechanisms. In uninephrectomized and NaCl 1% treated mice, the selective deletion of mineralocorticoid receptor expression on macrophages by Cre/LoxP-recombination prevents the overexpression of plasminogen activator inhibitor type 1 and NADPHox, which protect these animals from cardiac fibrosis [12]. Recently, it has been shown that the mineralocorticoid receptor expressed by myeloid cells contributes to modulating the phenotype of macrophages [50]. Mice lacking mineralocorticoid receptor in myeloid cells exhibited a transcription profile characterized by the expression of reparative and remodeling proteins [50]. *In vivo*, mineralocorticoid receptor deficiency in macrophages mimicked the effects of mineralocorticoid receptor antagonists and protected against cardiac hypertrophy, fibrosis, and vascular damage caused by N^{ω}-nitro-L-arginine methyl ester and angiotensin-II (Ang-II) [50]. The development of hypertension, hypertrophy, and fibrosis of the heart and aorta seems to be critically dependent on the activation of the mineralocorticoid receptor expressed by myeloid cells. Accordingly, it has been recently shown that mineralocorticoid receptor ablation in cardiomyocytes, but not in fibroblast, protects from cardiac dilatation and failure after chronic pressure overload [51]. In this study, neither interstitial or perivascular fibrosis, nor macrophage infiltration and inflammation were affected, suggesting differential functional pathways activated by the mineralocorticoid receptor, depending on the specific cell type [51,52]. Whereas mineralocorticoid receptor deletion in cardiomyocytes protects from heart failure after chronic pressure overload, mineralocorticoid receptor deletion in macrophages reduces immune cell infiltration, oxidative stress production, and inflammation. A model for the possible mechanisms of modulation of innate immune cells and endothelial tissue by aldosterone is schematized in Fig. 1.

Modulation of adaptive immunity by aldosterone

In contrast to innate immunity, adaptive immunity consists of a highly variable repertoire of antigen receptors expressed on the surface of $CD4^+$ and $CD8^+$ T cells (cellular response) and B cells (humoral response), which recognize infected host cells and microbial pathogens. Cellular immunity can be divided into distinct responses based on the cytokine pattern secreted by $CD4^+$ T cells. Whereas Th1 T cells mainly secrete IFN-γ, Th2 cells produce IL-4 and IL-10 [53]. Recently, a new population of $CD4^+$ T cells has been characterized by the production of IL-17 and denominated as Th17 [54,55]. This newly described Th17 immune response has been associated with the clearance of diverse pathogens, as well as with the development of some autoimmune-inflammatory disorders, such as multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus [56–61].

The involvement of adaptive immunity, specifically T cells, in the development of the vascular dysfunction induced by mineralocorticoids has been recently suggested [62–64]. This notion is supported by the striking observation that mice deficient in the recombinase-activating gene (RAG), which lack both T and B lymphocytes, are resistant to the hypertensive response induced by either the mineralocorticoid deoxycorticosterone acetate (DOCA)-salt or Ang-II. The adoptive transfer of T cells, but not B cells to these mice, restored the susceptibility to developing hypertension and vascular damage [62]. Ang-II also increased T-cell activation, vascular infiltration, and O_2^- production *in vivo* [62]. Furthermore, a recent study described that Ang-II infusion during 4 weeks increased IL-17 production from T cells and IL-17 protein in the aortic media [65]. Interestingly, hypertension was not sustained in IL-$17^{-/-}$ mice as compared to wild-type mice. Contrasting with wild-type mice infused with Ang-II, arteries from IL-$17^{-/-}$ mice displayed preserved vascular function, decreased superoxide production, and reduced T-cell infiltration in response to Ang-II. Thus, T cells are likely to play a central role in modulating hypertensive response and vascular dysfunction induced by high levels of Ang-II-aldosterone. A recent study has provided evidence that hypertension promoted by peripheral Ang-II infusion can be prevented by blocking central action of the hormone on central nervous system (CNS) through lesions at the third cerebral ventricle [66]. The CNS lesions also

Fig. 1



High aldosterone levels trigger different responses on endothelial and inflammatory cells. (a) Through a mineralocorticoid receptor-dependent mechanism, excessive aldosterone production can trigger in monocytes the expression of mineralocorticoid response elements (MREs), such as NADPH oxidase (NADPHox) and inducible nitric oxide synthase (iNOS). These enzymes promote in turn the production of reactive oxygen species, including peroxonitrite (ONOO) and superoxide anion (O_2-). Additionally, aldosterone interaction with mineralocorticoid receptor induces on endothelial cells expression of MREs, such as NADPHox expression and O_2- production. Aldosterone also promotes endothelial nitric oxide synthase (eNOS) uncoupling, which triggers O_2- production. (b) In response to aldosterone, endothelial cells express intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 that promote the attachment of immune cells by binding to lymphocyte function-associated antigen (LFA)-1 and very late antigen (VLA)-4, respectively. Aldosterone also induces monocyte chemoattractant protein (MCP)-1 production by endothelial cells, a protein that promotes the recruitment of leukocytes by interacting with chemokine (C-C motif) receptor 2 (CCR2). Monocyte/macrophages produce IL-1β and IL-1β receptor and promote the expression of more adhesive molecules on inflammatory cells. (c) LFA-1/ICAM-1 mediates macrophage/monocyte extravasation. MCP-1 induces immune cells recruitment, increasing thus leukocyte infiltration.

abolished T-cell activation and vascular inflammation [66]. These results indicate a mechanism independent of the direct modulation of Ang-II on T-cell activity. Considering that T-cell activation and vascular inflammation in these experiments were abolished by hydralazine, it was proposed that high blood pressure is an initial step leading to vascular inflammation and T-cell activation in hypertension [66]. Another study showed that intracerebroventricular infusion of eplerenone, spironolactone, or aldosterone synthase inhibitor can attenuate the Ang-II-induced hypertension in rats, suggesting that local brain production of aldosterone and brain mineralocorticoid receptor activation could contribute to Ang-II-induced hypertension [67]. In addition, the cross-talk between Ang-II-induced and aldosterone-induced signaling pathways has been recently described [68]. Accordingly, the intracerebroventricular administration of mineralocorticoid receptor blockers can prevent cardiac fibrosis and improve kidney function after myocardial infarction, suggesting that mineralocorticoid receptor signaling in the CNS promotes cardiac and kidney damage [69,70]. The mechanism responsible for the profibrotic effect of aldosterone on the brain seems to involve the modulation of pro-inflammatory cytokine release into the circulation, such as tumor necrosis factor-α (TNF-α), cyclooxygenase-2, and prostaglandin E2 and the activation of sympathetic nervous system [71]. Thus, there is an intriguing and still not fully understood field involving aldosterone-mineralocorticoid receptor activation in the CNS and lymphocyte activation. Further research is needed to assess the relative contribution of this pathway to T-cell function.

Because dendritic cells, professional antigen-presenting cells that are able to interact with naïve T cells, are required for the activation of $CD8^+$ and $CD4^+$ T cells, as well as for the polarization of $CD4^+$ T cells, it is possible that these cells could also contribute to the onset of hypertension and cardiac damage induced by DOCA and aldosterone [72]. Thus, we have recently shown that aldosterone can modulate dendritic cell function increasing their capacity to prime $CD8^+$ and $CD4^+$ T cells and inducing the polarization of $CD4^+$ T cells into Th17 cells, through the selective secretion of IL-6 and TGF-β by dendritic cells [73]. These effects can be prevented by eplerenone and spironolactone [73]. Consistently with this notion, dendritic cells express functional mineralocorticoid receptor and receptor stimulation by aldosterone leads to p38 and JNK phosphorylation [73]. As part of experimental autoimmune encephalomyelitis (EAE), autoimmune disease characterized by exacerbated Th17 responses, aldosterone was shown to promote the production of IL-17 by $CD4^+$ T cells leading to an exacerbation of EAE symptoms [73].

These observations support the notion that the activity of T cells at promoting hypertension and cardiac damage in DOCA-salt induced hypertension could be in part due to an abnormal function of dendritic cells, during the priming of T cells and vascular infiltration. Supporting

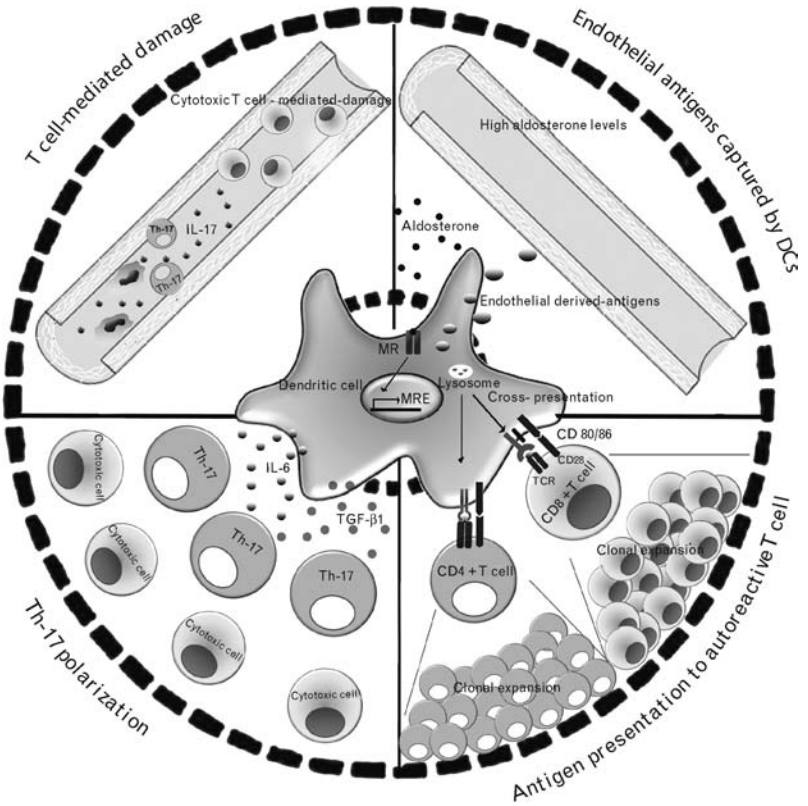
this hypothesis, dendritic cells have been detected in the aorta of mice, especially in the aortic valve and sinus [74]. These aortic dendritic cells are able to capture antigens and activate T cells [74]. It is likely that these aortic dendritic cells in presence of high levels of aldosterone could capture antigens present at the cardiovascular system, migrate to draining lymph nodes, and activate autoreactive antigen-specific T cells imprinting on them with a Th17 polarized phenotype. In addition, other cell types secrete IL-6 and TGF-β in response to aldosterone, which further promote a cytokine environment that drives Th17 polarization [75,76]. In agreement with this notion, eplerenone treatment reduces myocardial fibrosis in mice suffering from viral myocarditis and enhances their survival [77]. Because viral myocarditis has been recently associated with an increased Th17 response [78], it is possible that the immunomodulatory effect of eplerenone could be related to a decrease of Th17 polarization during this ailment. A schematic model for this process is shown in Fig. 2. However, further research is required to evaluate this hypothesis.

Immunological end-organ damage caused by aldosterone

Human studies

In humans, hypertension is one of the most important predictors of cardiovascular risk in population studies. Interestingly, approximately 15% of patients suffering from essential hypertension show an inappropriate regulation of aldosterone [79–81]. In primary aldosteronism patients, the prevalence of cardiovascular complications, such as left ventricular hypertrophy, is higher when compared to essential hypertension patients [82]. Furthermore, the expression of OPN, a phosphoprotein involved in vascular remodeling and immune cell activation, was higher in primary aldosteronism patients as compared to essential hypertension patients, suggesting that aldosterone may contribute to the cardiovascular complications of primary aldosteronism by inducing OPN expression [83]. In agreement with these findings, we have recently shown that primary aldosteronism patients display increased secretion of IL-10, TGF-β, and TNF-α, as compared to normotensive controls, and spironolactone

Fig. 2



Possible role of dendritic cells in cardiovascular pathogenesis induced by aldosterone. The increase of circulating aldosterone levels or local production of aldosterone by cardiovascular system, together with other stimuli, can promote the maturation of aortic dendritic cells by a mineralocorticoid receptor-dependent mechanism. At blood vessels, dendritic cells can internalize self or foreign antigens and migrate to draining lymph nodes to activate antigen-specific $CD8^+$ and promote Th17 polarization of $CD4^+$ T cells through IL-6 and transforming growth factor-β (TGF-β) secretion. Finally activated T cells could migrate to vascular system promoting vascular damage through reactive oxygen species (ROS) production, pro-inflammatory cytokines secretion, and additional recruitment and activation of immune cells.

only partially restored these levels [84]. Compared with essential hypertension patients, primary aldosteronism patients showed significantly reduced TGF-β1 and TNF-α serum levels [84]. These data suggest that primary aldosteronism patients could have altered immune-inflammatory responses and that aldosterone could modulate innate immune response through promotion of leukocyte adhesion and the production of ROS.

Regarding the adaptive immune response and Th17 polarization, gene array analyses of cultured human aortic smooth muscle cells have revealed that IL-17 together with TNF-α can modulate the expression of over 30 genes, including several inflammatory cytokines/chemokines [65]. The relevance of IL-17 in hypertension is further suggested by the observation that serum levels of IL-17 in 112 diabetic patients showed a significant increase on those patients suffering from hypertension, as compared to normotensive diabetic individuals [65]. Thus, it is justified to speculate that Th17 cells could in turn contribute to the inflammatory damage observed in primary aldosteronism patients. Further research is required to evaluate this possibility.

Mineralocorticoid receptor-independent mechanisms in the modulation of immune responses

In addition to the mineralocorticoid receptor-dependent modulation of the immune response by aldosterone, several studies have shown that some of the effects of this hormone cannot be blocked by spironolactone or eplerenone. These data suggest that aldosterone might have mineralocorticoid receptor-independent mechanisms for influencing immune cell function [85]. For instance, in human embryonic kidney (HEK) cells and VSMCs, aldosterone triggers a rapid and transient increase of cytosolic Ca^{2+} that cannot be reverted by spironolactone [85,86]. Similar results have been observed in murine models, in which rapid increases in cAMP and intracellular calcium levels are induced by aldosterone in mineralocorticoid receptor-knockout mice [87]. These results suggest that a distinct and unidentified receptor may interact with aldosterone and trigger mineralocorticoid receptor-independent effects. Although the putative receptors have not been fully elucidated, some studies have hinted at the pertussis toxin-sensitive heterotrimeric G proteins family as one of the possible candidates mediating the mineralocorticoid receptor-independent effect of aldosterone [88]. Accordingly, elastin, an important component of extracellular matrix that provides resilience to many tissues, is expressed by human cardiac fibroblasts in response to aldosterone through a mineralocorticoid receptor-independent mechanism involving heterotrimeric G protein Gα13 activation and PI 3-kinase/Akt signaling [89]. Although no mineralocorticoid receptor-independent mechanism has been described in immune cells, it is likely the only partial capacity of spironolactone to revert aldosterone-induced cytokine production in primary aldosteronism patients could be due to noncharacterized mineralocorticoid receptor-independent effects on immune cells.

Novel immunomodulatory molecules for the prevention of aldosterone-induced cardiovascular damage

Considering the potential importance of the innate and adaptive immune responses in the genesis and progression of the cardiovascular disease induced by aldosterone, it is possible that several immune-suppressor molecules could be useful for the treatment of this disorder. Alternatively, it is possible that aldosterone receptor antagonists could mediate their beneficial effects in part by modulating the immune response. According to this hypothesis, the addition of spironolactone or eplerenone to existing therapy decreased morbidity and mortality in patients with heart failure [16,17]. Moreover, different studies have shown attenuated expression of proinflammatory molecules in hearts of uninephrectomized rats receiving 1% NaCl and aldosterone when these molecules are added [46,90]. Recently, we have shown that both aldosterone blockers are able to abolish the $CD8^+$ T-cell activation and Th17 polarization of $CD4^+$ T cells in mice, which is in agreement with a possible immune-suppressor effect for spironolactone and eplerenone [73]. As a corollary, it is possible that other immunomodulatory molecules could be potentially useful for treating cardiovascular inflammatory disease. As an example, the angiotensin AT1 receptor antagonist valsartan can also reduce the risk for the combined end point of mortality and morbidity in patients with heart failure [91]. Due to the fact that this molecule exerts an inflammation-suppressive effect by downregulating ROS production and NF-κB activation in leukocytes, it is probable that the blockade of innate immunity could explain the observation of valsartan-prevention of cardiovascular complications in patients with heart failure [92]. Another examples are statins, inhibitors of 3-hydroxy-3-methylglutaryl CoA reductase, which have been associated with the reduction of cholesterol synthesis, antiatherogenic, and tissue-protective functions, and thus, widely used in the treatment of cardiovascular diseases [93]. Statins have been shown to inhibit T-cell activation and also the recruitment of regulatory T cells [94–96]. Statins are also involved in the inhibition of macrophage infiltration and proliferation by modulating the expression of IL-10 and heme oxygenase-1 on these cells [72,97]. Thus, the anti-inflammatory and immunomodulatory properties of these molecules could explain in part their beneficial effects on cardiovascular diseases.

Perspectives

Increasing evidence in the last decade has shown that several of the deleterious effects of elevated aldosterone levels could be mediated by an exacerbated

immune response. Innate and adaptive immune responses are modulated by aldosterone, which promotes ROS and inflammatory cytokine production and vascular infiltration. The EPHESUS and RALES studies have demonstrated that the addition of mineralocorticoid receptor inhibitors to standard therapy for chronic heart failure patients promotes reduction in morbid and mortal events in patients with heart failure, which could be associated with a diminished production of ROS by immune cells. Moreover, mineralocorticoid receptor expression by immune cells, such as dendritic cells, has opened a new window of possibilities of interaction between the endocrine and immune system. Our group has shown that blockade of NF-κB function on dendritic cells can significantly enhance their tolerogenic capacity [98]. The treatment of dendritic cells with two different drugs – roziglitazone or andrographolide – is able to interfere with the activation of NF-κB, rendering dendritic cells unable to mature in response to lipopolysaccharide and to activate antigen-specific T cells *in vitro* and *in vivo* [99]. Due to the contribution of adaptive immunity to cardiovascular damage mediated by aldosterone and to the importance of NF-κB for the function of immune cells, it is possible that addition of immunomodulator drugs to existing therapies might contribute to reduction in morbidity and mortality in hypertensive patients. Accordingly, we observed that neither spironolactone nor eplerenone was able to inhibit dendritic cell function [73]. Because immunomodulatory molecules, such as roziglitazone and andrographolide, can inhibit dendritic cell maturation and T-cell activation, it is possible that combination of mineralocorticoid receptor blockers and immunomodulators could efficiently work as therapy to downmodulate adaptive immunity by targeting different immune cells [98]. Moreover, due to the known side-effects of spironolactone (breast tenderness and menstrual irregularities in women, and impotence, decreased libido and gynecomastia in men) and the high cost of eplerenone, it is likely that the use of combined immunomodulator drugs together with mineralocorticoid receptor blockers could provide cardiovascular benefits and also contribute to diminishing the drug doses in primary aldosteronism patients. Further studies in patients are required to confirm this hypothesis. At present, we can propose that innovative immunological biomarkers could be developed in the next future to prevent the onset and progression of vascular injury in such settings as congestive heart failure and hypertension.

Acknowledgements

Conflicts of interest

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A patent application has been filed on the use of spironolactone to treat multiple sclerosis.

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