REVIEW

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Targeting inflammation in hypertension

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Purpose of review
Hypertension remains a global health and socioeconomic burden. Immune mechanisms are now recognized as integral part of the multifactorial etiology of hypertension and related organ damage. The present review addresses inflammatory pathways and immune targets in hypertension, which may be important for an immunomodulatory treatment of hypertension aside from lowering arterial pressure.

Recent findings
Anti-inflammatory interventions targeting single interleukins or almost the entire immune system show different beneficial effects. While immunomodulation (targeting specific portion of immune system) shows beneficial outcomes in certain groups of hypertensives, this does not pertain to immunosuppression (targeting entire immune system). Immunomodulatory interventions improve outcomes of hypertension independent of arterial pressure. The studies reveal interleukins, such as interleukin (IL)-1β and IL-17 as targets of immunomodulation. Besides interleukins, targeting αvβ-3 integrin and matrix metalloproteinase-2 or using experimental cell-therapy demonstrate beneficial effects in hypertensive organ damage. The NLR family pyrin domain containing 3 (NLRP3) inflammasome/IL-1β/endothelial cell/T-cell axis seems to be an important mediator in sustained inflammation during hypertension.

Summary
Although immunomodulation may be advantageous as a causal therapy in hypertension, targeting immune networks rather than single interleukins appears of major importance. Further research is required to better identify these networks and their links to human hypertension.

Keywords
arterial pressure, hypertension, immunomodulation, inflammation, target organ damage

INTRODUCTION

Hypertension is the number one noninfectious cause of mortality, which largely surpasses other important factors of mortality such as smoking and metabolic diseases [1,2]. Hypertension is a leading risk factor for myocardial infarction, stroke, kidney damage and cognitive impairment. Almost 1.5 billion people worldwide have hypertension, the vast majority of them with primary/essential hypertension and a smaller fraction with secondary hypertension [1,2]. This pandemic nature of hypertension prevalence exerts tremendous health and socioeconomic burdens worldwide. In the year 2019, hypertension was responsible for almost 20% of all deaths [3]. The prevalence of hypertension and related death toll caused by its complications show no signs of slowing down. An updated classification of hypertension in the United States in 2018 categorized almost half of the population as hypertensive [4]. Although pharmacological treatment of hypertension started five decades ago, still today the desired blood pressure range is not achieved in almost every second patient receiving treatment. An additional problem is caused by resistant hypertension where compliant patients taking up to five antihypertensive agents are unable to control their blood pressure. Poor control of blood pressure despite of availability and use of various antihypertensive agents indicates that important pathophysiological mechanisms of hypertension are still not well understood. The understanding of the multifactorial causality of arterial hypertension dates back to Dr Page, who in 1949 proposed his Mosaic Theory, which proposed the

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KEY POINTS

- Besides revealing inflammatory cells and interleukins contributing to hypertension and related organ damage, more mechanistic incites appear on how immune network operates in hypertension.
- Experimental immunomodulatory interventions reveal that beneficial effects on target organ damage in hypertension are independent of arterial pressure.
- Several inflammatory markers shown to be helpful in identifying high risk patients who may especially benefit from immunomodulatory intervention in hypertension.

importance of kidneys, vasculature and heart, along with the central nervous system in development of hypertension (revised in 1982 [5]). The immune system can be considered as an integral part of this Mosaic Theory as the role of inflammatory cells in hypertension has been implicated since the early 1960s. However, it was only in 2007 that a causal role of T cells in hypertension and target organ damage was demonstrated [6]. Since then multiple immune cell types and cytokines have been implicated in the pathogenesis of hypertension. Cell subtypes of both innate and adaptive immune systems, especially macrophages, γδ, $CD4^+$ and $CD8^+$ T cells and, along with interleukins interleukin (IL)-6, IL17A, IL-1β and interferon (INF)-γ have been suggested to mediate development of hypertension and target organ damage. Several clinical anti-inflammatory trials such as CANTOS [7], CIRT [8] and LoDoCo2 [9,10] gave promising but still inconclusive findings. However, they underline the advantageous importance of targeting specific portion of immune system, e.g. interleukins (immunomodulation) over suppression of entire immune system (immunosuppression). It is hoped that advancing the knowledge of inflammatory pathways in hypertension will strengthen the causal treatment of hypertension and better prevent organ damage.

IMMUNOLOGY OF HYPERTENSION

Interleukins and renal inflammation

Renal inflammation is considered a major contributor to development of hypertension, including salt-sensitive hypertension [11]. Multiple interleukins, along with IL-1β, are elevated in kidneys of hypertensive animals. Vieras *et al.* [12▪] investigated the mechanism of IL-1β in renal inflammation and promotion of salt-sensitive hypertension in diabetic mice. These mice had higher levels of IL-1β in renal tubule cells than their nondiabetic controls. Isolated renal tubular epithelial cells of these diabetic mice released high levels of IL-1β in response to glucose stimulation. Besides revealing the source of IL-1β, the authors demonstrate that IL-1β polarizes resident microphages to a pro-inflammatory cell type, which in turn released IL-6 promoting inflammation. Importantly, blockade of IL-1 receptor seemed to protect the mice from not only renal inflammation but also reduced expression of epithelial sodium channels and mean arterial pressure. In regard to IL-1β, a secondary analysis of CANTOS revealed that inhibition of IL-1β does not decrease blood pressure, but reduces major cardiovascular events [13]. Thus, the cardiovascular beneficial effects were achieved without a reduction of arterial pressure, which is an important finding strengthening the conceptual role of anti-inflammatory interventions to protect target organ damage, without affecting arterial pressure. Expression of epithelial sodium channels (ENaC) seem to be affected by the IL-1β/IL-6 axis (Fig. 1). In male mice exposed to 4 weeks of high salt treatment, IL-6 mediated inflammatory response impairs downregulation of ENaC in response to high salt and promotes salt-sensitive hypertension [14]. Inhibition of inflammation or specific blockade of IL-6 prevented development of salt-sensitivity and reduced mean arterial pressure. Interestingly, these findings were specific for male mice, whereas the inflammatory response toward IL-6 was absent in female mice. While this study shows a role of IL-6 in development of salt-sensitive hypertension, it importantly demonstrates a sexual dimorphism in salt sensitivity.

Lu *et al.* [15] reported that both renal and plasma levels of IL-22 were elevated in patients with hypertensive renal injury (HRI). Wang *et al.* [16] investigated the mechanisms of IL-22 in mediation of angiotensin-II (ANGII)-induced hypertensive renal injury (HRI). IL-22 acted via the JAK2/STAT3 pathway leading to renal inflammation and fibrosis, along with an increased blood pressure response toward ANGII. Infusion of recombinant IL-22 leads to similar adverse effects in kidneys and elevated blood pressure. This is particularly interesting, because, although a role of IL-17 has been established in many models of experimental hypertension as well as in patients [17], Thangaraj *et al.* [18] demonstrate that infusion of IL-17 does not increase arterial pressure in mice. Although IL-22 infusion caused adverse effects, it is hardly conceivable that it acted alone. Various hypertensive stimuli may establish a network of multiple interleukins with various interactions.

Hypertensive patients also have elevated levels of IL-18 [19]. Thomas *et al.* [19] investigated the role and mechanism of IL-18 in hypertensive renal

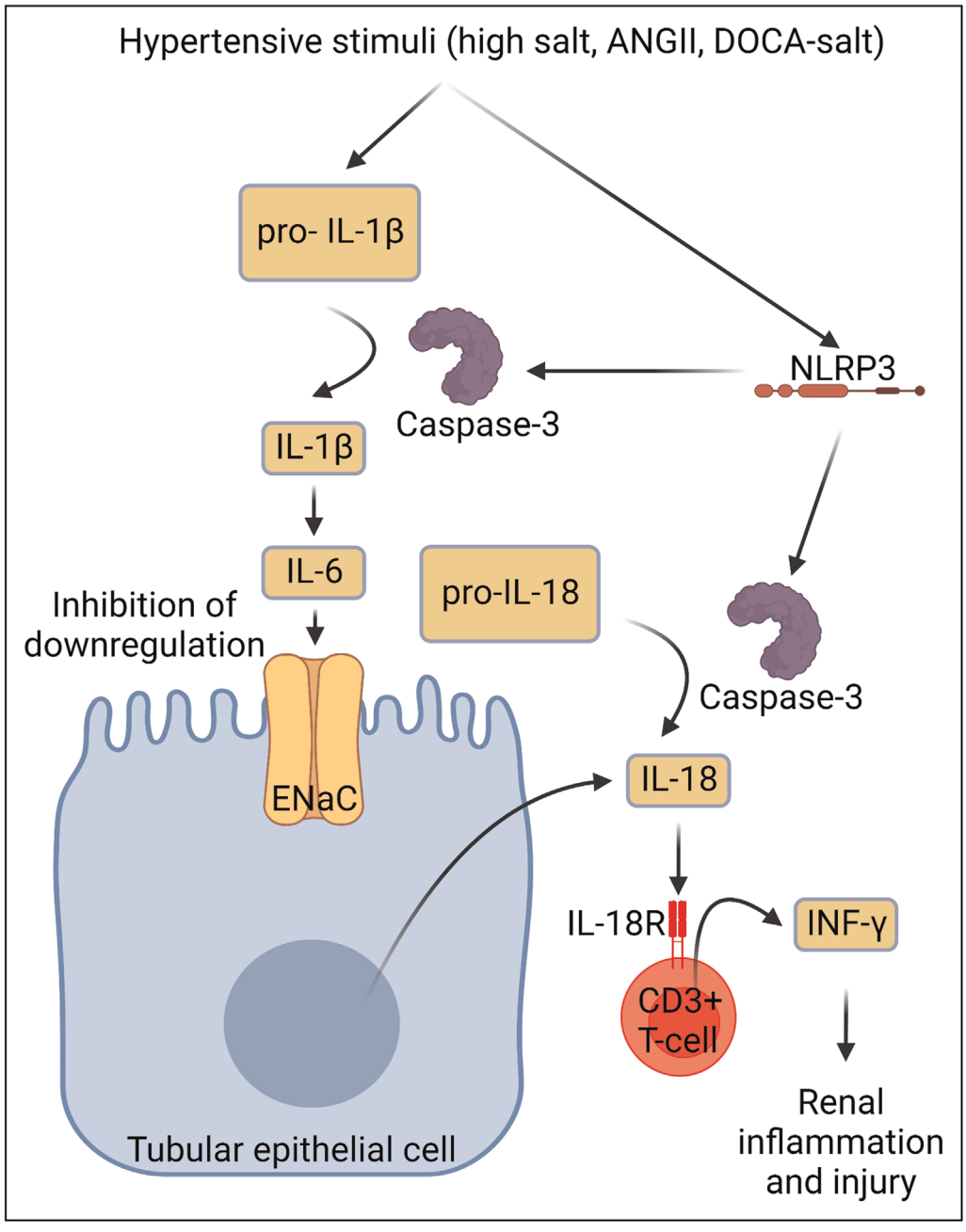

FIGURE 1. Schematic model of interleukin interaction in mediation of hypertensive renal inflammation and injury.

injury. In the Deoxycorticosterone Acetate-salt hypertension model, renal tubular epithelial cells produced IL-18, which acted on IL-18R on $CD3^+$ T cells, which in turn produce INF-γ (Fig. 1). Subsequently, IL-$18^{-/-}$ mice were protected from hypertension-induced renal inflammation and fibrosis, as well as elevation of systolic blood pressure. Notably, both IL-1β and IL-18 are activated by caspase-1 via catalytic cleaving from their latent pro forms [19]. Caspase-1 is activated by NLR family pyrin domain containing 3 (NLRP3) inflammasome which mediates development of experimental and clinical inflammatory renal injury during hypertension [19,20]. This mechanistic axis activating IL-1β seems to also be important in ANGII-induced cardiac fibrosis [21]. Here ANGII via its AT1R activates the PLC/IP3R/Ca^{2+} pathway triggering the NLRP3 inflammasome assembly and caspase-1 activity, along with increased IL-1β levels.

Interplay of antigen presenting-, endothelial- and T-cells

Inflammatory cells of both innate and adaptive immune systems play a major role in development of hypertension and target organ damage. Here,

antigen-presenting cells (APCs) play a central role in activation of the adaptive T-cell response in hypertension. The NLRP3 inflammasome of APCs responds with activation to salt stimulation in an epithelial sodium channel- and IsoLGs (isolevuglandins)-dependent manner [22▪]. Activated NLRP3 then employs the aforementioned mechanism upregulating IL-1β, which polarizes T-cells to produce excess IL-17 and INF-γ (Fig. 2) [23]. CD36, a scavenger receptor, seems to also be involved in the mediation of NLRP3 activation [24]. However, CD36 increases reactive oxygen species and decreases AMP-activated protein kinase activity, which in turn increases NLRP3 activity and IL-1β levels. In ANGII-induced hypertension, the NLRP3 activation of APCs causes endothelial dysfunction [25]. Increases in NLRP3 and IL-1β in these models resulted in a decreased phosphorylation of Endothelial nitric oxide synthase (eNOS)-Ser1177, which impaired NO production. While NLRP3 is an important activator of IL-1β, it is unlikely that IL-1β directly caused the decrease in eNOS phosphorylation, but rather acted via IL-17. As mentioned above, IL-1β triggers IL-17 production from polarized T-cells [23]. This interleukin reduces NO production by increasing phosphorylation of the inhibitory eNOS residue Thr495 via activation of RhoA-kinase, while decreasing phosphorylation of activator eNOS residue Ser1177 [26]. Therefore, the NLRP3/IL-1β/T-cell derived IL-17 is most likely responsible for impaired eNOS phosphorylation/NO production and endothelial dysfunction (Fig. 2). This may be interpreted as an orchestrated effect to facilitate inflammatory recruitment in target organs during hypertension. While it is obvious that T-cells mediate their effects via production of multiple cytokines, less is known about the mechanisms, which regulate this process. Nosalski *et al.* demonstrate that T-cell derived miR-214 regulates the production of several profibrotic cytokines, such as IL-17, INF- γ, tumor necrosis factor (TNF)-α, IL-9 and a number of chemokines, which mediate perivascular fibrosis in ANGII-induced hypertension [27]. miR-214$^{-/-}$ mice were protected from endothelial dysfunction and oxidative stress. By regulating chemokines and mediating endothelial dysfunction, miR-214 triggers further T-cell recruitment and promotes T-cell inflammation (Fig. 2). In fact, in hypertensive patients, plasma miR-214 levels were correlated with increased pulse wave velocity [27]. Besides classical effector CD4^{+} and CD8^{+} T-cells, which mediate hypertensive organ damage, memory T-cells are also a source of IL-17 and INF-γ, triggering elevation in blood pressure after repeated hypertensive stimuli [28,29]. Itani *et al.* [30▪] critically addressed the role of these memory T-cells by using fingolimod, which antagonizes Sphingosine-1-phosphate receptor (S1PR). By inhibiting S1PR, egress of effector memory T-cells from bone marrow was attenuated and mice were protected from hypertensive kidney injury. Mice treated with the S1PR inhibitor could not sustain hypertension compared to untreated mice. Hereby the authors demonstrate that repeated hypertensive stimuli lead to mobilization of memory T-cells from bone marrow, which may contribute to predisposition to hypertension and target organ damage [30▪].

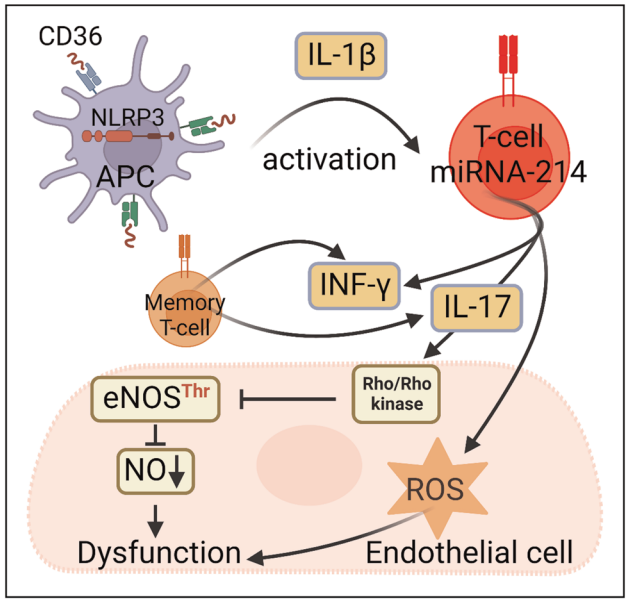

FIGURE 2. Cross-talk of APC and T-cells, as well as role of memory T-cells in mediation of endothelial dysfunction during hypertension. APC, antigen-presenting cell.

IMMUNE TARGETS IN TREATMENT OF HYPERTENSION

An anti-inflammatory therapy in hypertension can be classified into immunomodulatory (or anticytokine) and immunosuppressant. The large CANTOS trial demonstrated that although the IL-1β antagonist canakinumab reduced combined major adverse cardiovascular event rates (myocardial infarction, revascularization, stroke, heart failure) versus placebo, it did not reduce incident hypertension [13]. However, treatment also increased the incidence of fatal infections. Other human studies with anticytokine approaches blocking IL-6 [31,32] or IL-17 [31,32] reported no change in arterial pressure in response to treatment. In a trial with the immunosuppressant methotrexate (CIRT), treatment did not decrease the levels of IL-1β and IL-6 or blood pressure and cardiovascular events. However, the treatment resulted in adverse effects in liver, blood and skin [8]. Concerning immunomodulation, Failer

et al. [33] demonstrated potent effects of the endogenous anti-inflammatory factor DEL-1 (developmental endothelial locus-1) in two distinct models of experimental hypertension (Fig. 3). Even after established hypertension in mice, injections of recombinant DEL-1 ameliorated cardiovascular inflammation and remodeling. Although systolic blood pressure was lower in treated mice at the end of the treatment period, beneficial effects of DEL-1 on organ damage were not attributed to the reduced arterial pressure, but rather to its anti-inflammatory actions. DEL-1 stabilized anti-inflammatory regulatory T-cells (Treg) and IL-10 levels, while it decreased pro-inflammatory cell recruitment and levels of pro-inflammatory cytokines including IL-17, IL-6 and IL-1β. It also blocked activation of matrix degrading proteinase MMP2. The mechanism of action of DEL-1 was largely attributed to its interaction with αvβ-3 integrin [34], which is an important regulator of Treg function and activation of MMP2 [35]. Knockdown of MMP2 also attenuated age dependent carotid stiffening by improving endothelial function in mice, which is the limiting factor for propagation of inflammation [36]. Further, experimental TNF-α inhibition protected spontaneously hypertensive rats from renal injury without affecting arterial pressure [37]. Józefczuk *et al.* [38] reported that ANGII-infused mice treated with a Sphk1 (sphingosine kinase 1) inhibitor were protected from cardiac inflammation and fibrosis, which was associated with downregulation of multiple factors including STAT3, PKC ERK1/2 and Rock1. Again, no effects on arterial pressure were observed. Experimental cell therapy with cardiosphere-derived cells (CDCs) improved endothelial function by enhancing nitric oxide production and inhibiting expression of endothelial pro-inflammatory molecules like

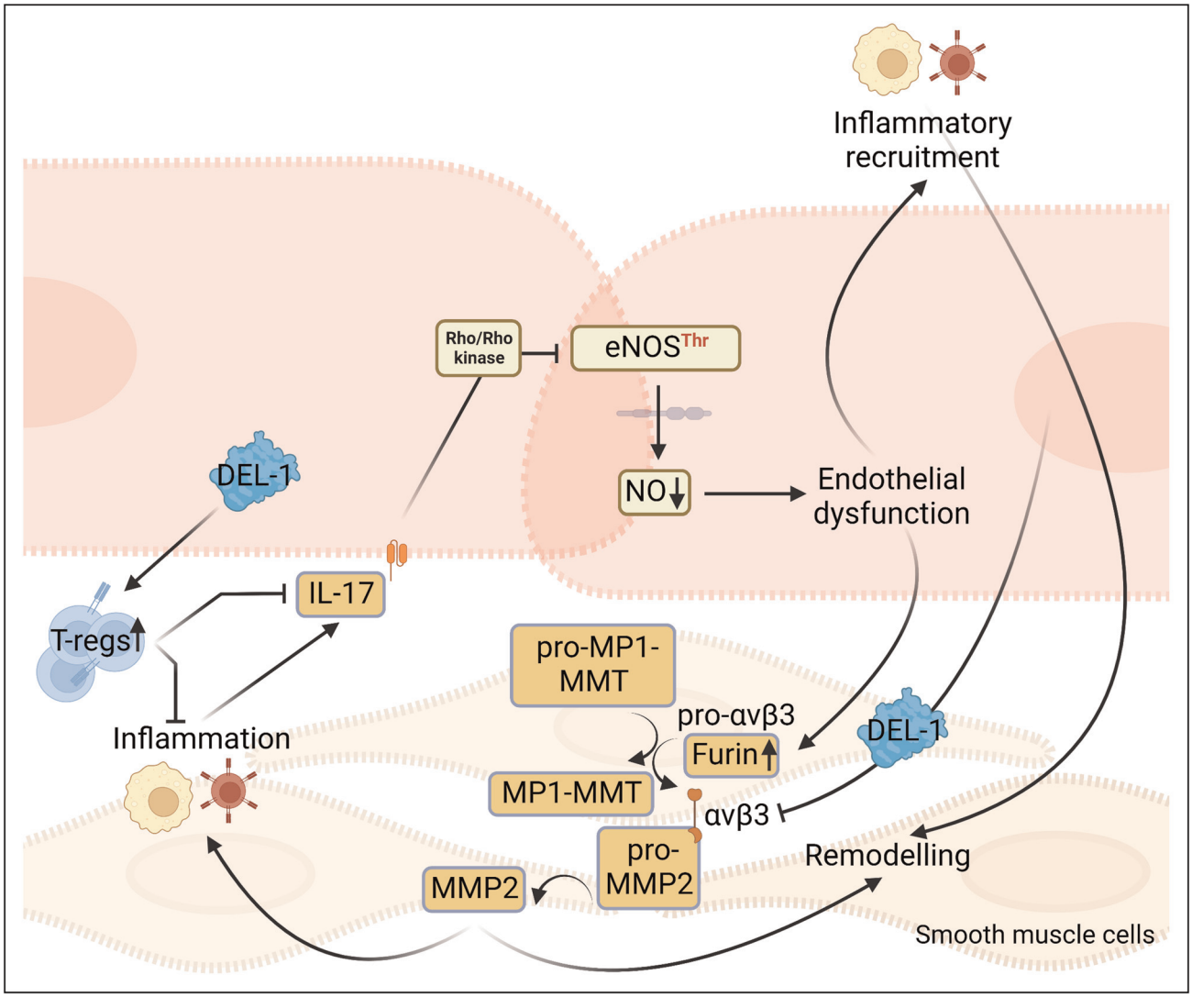

FIGURE 3. Model mechanisms of anti-inflammatory actions of DEL-1 in hypertension. DEL-1, developmental endothelial locus-1.

Vascular cell adhesion protein 1 [39]. CDCs also decreased levels of IL-6 and IL-1β and protected from hypertension induced cardiac damage, without affecting arterial pressure.

INFLAMMATORY MARKERS IN HYPERTENSION

It is a still unresolved issue whether potential anti-inflammatory interventions in hypertension can be applied generally to a hypertensive population or should rather be limited to specific groups of hypertensive patients. A secondary analysis of CANTOS pointed to the greater reduction of cardiovascular complications in the group of patients with highest blood pressures and possibly with the highest inflammatory state [13]. Because it is not settled whether an increase in arterial pressure necessarily correlates with augmented immune activity, identifying inflammatory markers, which may reveal high-risk patients, seems important. Several pro-inflammatory markers, including IL-17, IL-6, IL-1β, TNF-α, IL-23 were found elevated in hypertensive patients [40,41]. However, Mossmann *et al.* [42] reported the intriguing finding that the IL-6 level, which was measured in patients before undergoing angiography due to stable chest pain, can be used as a predictive marker for combined major cardiovascular events (myocardial infarction, stroke, heart failure, revascularization, cardiovascular [CV] death). Patients with IL-6 levels >0.44 pg/ml showed poorer prognosis, whereas those with IL-6 levels below this threshold showed better prognosis. Conversely, not all markers can be taken as prognostic markers despite of being associated with cardiovascular diseases. For example, miRNA-21, which has been shown to be increased in patients with hypertension and high cardiovascular risk, did not change despite a reduction in cardiovascular risk in patients after correction of hypovitaminosis D [43]. This demonstrates that thorough selection of markers is needed for precise prognosis of disease development in patients with hypertension. To improve cardiovascular risk stratification, multiple working groups of the European Society of Cardiology recommend that besides classical pro-inflammatory markers endothelial function should be assessed via flow-mediated dilatation [44]. This functional assessment seems important because the healthy endothelium counteracts, whereas a dysfunctional endothelium supports tissue remodeling as result of the local inflammatory response. Dysfunctional endothelium converts classical CD14þþ/$CD16^{low}$ monocytes to $CD14^{++}CD16^{+}$ intermediate monocytes via activation of STAT3 and leads to increased production of multiple pro-inflammatory cytokines [45].

CONCLUSION

Revealing immune mechanisms in the pathophysiology of hypertension has clearly expanded its already multifactorial etiology. A precise characterization of the underlying immune mechanisms may create new possibilities to treat hypertension causally. Lowering arterial pressure will undoubtedly remain an important target of the therapy, but improved understanding of immune mechanisms shifted the accent from a simply pressure related cause of hypertension to a mechanistic insight into causes of related organ damage. First experimental and clinical intervention studies clearly point to the fact that targeting the immune system in hypertension may have beneficial outcomes on various organ systems independent of lowering arterial pressure. The clinical studies also suggest that attempts of immunosuppression or immunomodulation with a single target may not be sufficient and may even be detrimental. Therefore, further unraveling inflammatory markers and their interactions in immune networks is crucial for more efficient immunomodulation of hypertensive disease.

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Conflicts of interest

There are no conflicts of interest.

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