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The immune system and hypertension

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Abstract

A powerful interaction between the autonomic and the immune systems plays a prominent role in the initiation and maintenance of hypertension and significantly contributes to cardiovascular pathology, end-organ damage and mortality. Studies have shown consistent association between hypertension, proinflammatory cytokines and the cells of the innate and adaptive immune systems. The sympathetic nervous system, a major determinant of hypertension, innervates the bone marrow, spleen and peripheral lymphatic system and is proinflammatory, whereas the parasympathetic nerve activity dampens the inflammatory response through $\alpha 7$ -nicotinic acetylcholine receptors. The neuro-immune synapse is bidirectional as cytokines may enhance the sympathetic activity through their central nervous system action that in turn increases the mobilization, migration and infiltration of immune cells in the end organs. Kidneys may be infiltrated by immune cells and mesangial cells that may originate in the bone marrow and release inflammatory cytokines that cause renal damage. Hypertension is also accompanied by infiltration of the adventitia and perivascular adipose tissue by inflammatory immune cells including macrophages. Increased cytokine production induces myogenic and structural changes in the resistance vessels, causing elevated blood pressure. Cardiac hypertrophy in hypertension may result from the mechanical afterload and the inflammatory response to resident or migratory immune cells. Toll-like receptors on innate immune cells function as sterile injury detectors and initiate the inflammatory pathway. Finally, abnormalities of innate immune cells and the molecular determinants of their activation that include toll-like receptor, adrenergic, cholinergic and AT1 receptors can define the severity of inflammation in hypertension. These receptors are putative therapeutic targets.

Keywords

Hypertension; Innate immune system; Toll-like receptors; Autonomic nervous system

Introduction

Hypertension is a chronic pathological state that afflicts about a third of the entire human population [1]. It is a major risk factor for premature cardiovascular disease, coronary and peripheral atherosclerosis, cardiac hypertrophy, heart failure, ischemic stroke, intracerebral hemorrhage and chronic and end-stage renal disease. More than ninety percent of the cases of hypertension do not have an identifiable cause and, therefore, are classified as essential or primary hypertension. Essential hypertension is thought to originate from the interaction between genetic and environmental factors.

The phenotypic manifestations of hypertension involve the central (CNS) and autonomic (ANS) nervous systems causing excessive sympathetic activation, the kidney with glomerular injury and the cardiovascular system with cardiac hypertrophy and vascular end-organ damage. The immune system plays a significant role in these events by inducing inflammatory processes in the CNS, the cardiovascular and the renal systems (Fig. 1). The magnitude and extent of the proinflammatory immune response may vary in different models of hypertension. Here, we will define the mechanisms linking the immune system to the hypertensive disease state. We will report studies in human hypertension as well as animal models of genetic hypertension (spontaneously hypertensive rat, SHR) and induced hypertension with deoxycorticosterone acetate/salt (DOCA/salt), angiotensin II (AngII) and renal damage.

Fig. 1

Schematic representation of sites of interactions between autonomic and immune systems. **A** Inflammation in the CNS induces autonomic activity, **B** autonomic-induced mobilization of hematopoietic progenitor and immune cells from bone marrow and spleen, **C** migration of immune cells into brain, vasculature, heart and kidney causing end-organ damage and **D** autonomic receptor and TLRs on immune cells interact to regulate cytokine release

Thymus plays a role in hypertension

The thymus is an important organ of the immune system that directs the maturation of T lymphocytes and ensures that immune responses are not self-targeted. Athymic (nude) mice do not develop the late chronic phase of deoxycorticosterone acetate (DOCA)-salt hypertension and exhibit decreased perivascular infiltration of immune cells following renal infarction [2, 3]. The SHR has normal blood pressure at birth and gradually develops high blood pressure after about 5 weeks of age that reaches maximal levels at about 15–20 weeks of age. Thymus transplant from neonatal normotensive Wistar rats to prehypertensive SHR delays the onset of hypertension from 5 weeks to 32 weeks and decreases the blood pressure in hypertensive adults [4]. Moreover, intraperitoneal injections of cell-free thymus extracts or thymosin α 7 also decrease blood pressure in adult hypertensive SHR [5].

Autoimmunity and IL-17 in hypertension

Several studies have reported increased serum immunoglobulins (IgG and IgA) in hypertensive patients [6–10]. There is high prevalence of hypertension in patients suffering

from the autoimmune disorder systemic lupus erythematosus (SLE) [11, 12] and in the experimental mouse model of SLE [13]. The highly proinflammatory cytokine IL-17 is a crucial player in several autoimmune diseases such as lupus and Crohn's disease [14, 15] and also plays a role in AngII-induced hypertension [16], which is not sustained in IL-17-deficient mice [17]. IL-17 can be responsible for inflammatory vascular disease and tissue damage [18].

The identity of specific immune cells in hypertension has not been well-defined [19]. IL-17 is predominantly produced by activated T lymphocytes known as Th17 cells as well as by natural killer cells (NK cells) and T cytotoxic (Tc) cells. Spironolactone, a mineralocorticoid receptor antagonist that acts downstream from AngII and reduces blood pressure, decreases Th 17 activation, whereas antihypertensive triple therapy (reserpine + hydralazine + hydrochlorothiazide) acting at different sites does not reduce Th17 activation [20].

In Dahl salt-sensitive rats, DOCA-salt increases T cell infiltration in the kidney including Th17 cells [21]. Treatment with anti-IL-17 antibodies significantly reduced arterial hypertension as well as expression of profibrotic and pro-inflammatory mediators and collagen deposits in the heart and kidney [20].

The polarization of T cells that are components of the adaptive immune system is dependent on the activation of monocytes, macrophages and dendritic cells, which form the innate immune system. In addition, complement factors are also involved in hypertension-related organ damage [22]. With the discovery of the new roles of the innate immune system and deeper understanding of the mechanism of immune response, the interest in immunological basis of hypertension is high.

The autonomic nervous system regulates the immune response

The ANS, which is composed of sympathetic and parasympathetic (vagal) innervation of the heart and the predominantly sympathetic innervation of the vascular system, is essential for the optimal circulatory adjustments to acute cardiovascular stresses. More recently, the importance of the ANS in the progression of chronic pathological changes in cardiovascular diseases has been recognized as being of major clinical and therapeutical significance. It is our premise that this chronic influence is principally due to the engagement of the immune system (Fig. 1).

The sympathetic nervous system is proinflammatory

In most hypertensive humans and animal models of hypertension, sympathetic nerve activity (SNA) is exaggerated [23-27] and contributes to increased mortality and morbidity [28, 29]. In addition, drugs and interventions that block or inhibit the sympathetic nervous system or the renin angiotensin system (RAS) are anti-hypertensive and prolong survival as does the activation of the vagal parasympathetic system [26, 27, 30, 31]. There is increasing evidence that the cardiovascular damage caused by excessive stimulation of the sympathetic and RAS and their receptors (α - and β -adrenergic and AngII AT1 receptors) is mediated through a proinflammatory activation of the immune system. Conversely, the protective effect of the

parasympathetic system and its $\alpha 7$ -nicotinic cholinergic receptors is through an anti-inflammatory immune response (Fig. 1).

Migration of innate or adaptive immune cells to the CNS can induce excitation of hypothalamic and paraventricular nuclei and caudal and ventrolateral medullary neurons causing central sympathoexcitation [32-35]. Sympathetic nerve fibers innervate both primary and secondary lymphoid organs such as thymus, bone marrow and spleen as well as the larger lymphatic system in the gut. Their activation increases mobilization and release of bone-marrow-derived progenitor cells into the circulation [36]. These immune cells may then home to the CNS causing a positive feedback enhancement of SNA directed to the heart, kidneys and vascular tissues exacerbating inflammation and end-organ damage [32, 33]. Thus, there is considerable bidirectional regulation between the ANS and the immune system [37]. Moreover, cytokinereleasing resident cells in various organs, such as glial cells in the CNS and mesangial cells in kidneys, have toll-like receptors (TLRs) and function as components of the immune system [38].

AngII enhances the immune response

Angiotensin II (AngII), a potent vasoactive peptide, is a major mediator of hypertension and target organ damage [19]. Intracerebro-ventricular infusion of AngII increases blood pressure and increases expression of proinflammatory cytokines in the spleen through central activation of the sympathetic nerves [39]. It induces proliferation of splenic lymphocytes and increases cytokine production through its action on AT1 receptors on immune cells [39-41] (Fig. 1). Several immune cells express components of RAS including AT1 receptors [42]. However, there are conflicting reports about the role of AT1 receptors on T lymphocytes [43]. Whereas mice with a global knockout of AT1-receptors are fully protected from AngII-induced hypertension [44], the T lymphocyte-specific conditional AT1-receptor knockout mice have elevated blood pressure and increased kidney damage similar to their wild-type (WT) controls [45]. On the other hand, dendritic cells lacking AT1 receptor have impaired TNF- α secretion [46].

Several studies have reported that AngII can induce cytokine expression and can be released from immune cells in an NF- κ B-dependent manner even though the mechanism of how AngII induces the NF- κ B is not understood. The in vivo effects of AngII may involve the mobilization and recruitment of immune cells that may lead to CNS infiltration of CD4 + T lymphocytes and exaggerated sympathetic nerve activation [47] as mentioned above. In the SCID (Severe Combined Immunodeficient) mice that lack lymphocyte responses, chronic AngII infusion results in a blunted hypertensive response, less cardiac hypertrophy and significant reduction in heart and kidney injury [48]. Results obtained in RAG1^{-/-} mice convincingly showed that the absence of T lymphocytes results in the abrogation of the AngII-induced hypertension [49]. Another compelling finding with AngII hypertension is its complete abrogation in IL-6^{-/-} mice [50], yet the renal vasoconstriction was unaltered. It appears that AngII-mediated phosphorylation of JAK2 and STAT3, which causes hypertension by enhancing tubular sodium reabsorption, is dependent on IL-6.

The parasympathetic (vagal) system is anti-inflammatory

The parasympathetic system, represented by the vagus nerve, has profound anti-inflammatory effect on its target organs as well as systemically. This effect is exerted by a 'cholinergic anti-inflammatory reflex' (CAR) whereby the CNS receives vagal afferent signals that may be induced by cytokines and reflexly stimulate the vagal efferents to negatively modulate the production of proinflammatory cytokines in the spleen through the $\alpha 7$ -nicotinic cholinergic receptors (nAChR) [51-53]. This anti-inflammatory action of the CAR was first described for the proinflammatory effects of bacterial lipopolysaccharides (LPS) that act through TLR4 on splenocytes [52-54].

The $\alpha 7$ -nAChR plays a major role in this anti-inflammatory circuit that is exemplified by its effect on LPS-induced cytokine production in the spleen [55, 56]. Although the spleen does not have direct vagal innervation, the anti-inflammatory reflex is likely mediated through an indirect mechanism involving nicotinic (nAChR) and muscarinic acetylcholine receptors (mAChR) on the lymphocytes, monocytes and macrophages [57-59]. It is likely that the CAR involves the efferent splenic noradrenergic sympathetic fibers that innervate ACh-producing immune cells in the spleen that then act in an autocrine/paracrine mode via nAChR to attenuate the LPS-induced cytokine production [60]. Moreover, activation of AChR plays a role in lymphocyte development and antibody production [61, 62]. The exact mechanism of this anti-inflammatory effect is not fully understood. However, it is clear that a dysregulated parasympathetic vagal (cholinergic) activity may diminish the anti-inflammatory control and enhance end-organ damage.

We have reported such a dysregulated cholinergic effect in the SHR where cholinergic stimulation with nicotine, in vitro and in vivo, results in enhanced proinflammatory cytokine production instead of the predictable anti-inflammatory effect (Fig. 1) seen in the normotensive WKY [63]. A comparable dysfunction of the cholinergic anti-inflammatory effect was shown by Li et al. [64] who reported a significant reduction in $\alpha 7$ -nAChR mRNA and protein in heart, kidney and aorta of SHR and rats with aortic coarction. Moreover, $\alpha 7$ -nAChR^{-/-} mice subjected to a two-kidney-one-clip procedure have more hypertension and end-organ damage with increased tissue levels of TNF- α , IL-1 β and IL-6, greater severity of glomerulosclerosis and proliferation of mesangial cells.

The renal immune response in hypertension

The effects of RAS activation on kidney function and role in hypertension have been extensively studied [65]. Here we will briefly look at the role of immune cells in the kidney in hypertension.

Immune cell infiltration in the kidney

T lymphocytes and macrophages infiltrate the kidneys in various models of hypertension [21, 22, 66]. In AngII-induced hypertension, complement activation and cell infiltration occur before the onset of albuminuria [67]. A role of autoimmunity in a model of renal infarction was demonstrated as early as in 1964 where injection of kidney extract in normal rat induced hypertension [68]. In the SHR, infiltration of T cells and macrophages and

increased NF- κ B activity in the kidney are observed at the prehypertensive age and progressively increases with age [69]. Pharmacological inhibition of proinflammatory transcription factor NF- κ B by a broad-spectrum inhibitor PDTC (pyrrolidine dithiocarbamate) normalized blood pressure in adult SHR and reduced immune-cell infiltration in the kidney [70].

Mesangial cells

Mesangial cells (MC) in the kidney constitute a large part of the glomerulus and are called the 'gatekeepers' owing to their essential function in maintaining homeostasis [71]. Cell proliferation and molecular changes in the extracellular matrix synthesis and deposition by MC occur in response to immunologic or hemodynamic injury [72]. In SHR, MC show greater proliferative activity than WKY even at prehypertensive age [73]. Such genetic abnormality may be one of the underlying causes of glomerular sclerosis observed in the SHR. These responses of MC are elicited through the activation of TLR and consequently production of cytokines, recruitment of macrophages and activation of complements [71]. The TLR activation is thought to be induced by damage-associated molecular patterns (DAMPs) originating from cellular debris of dying glomerular cells. A small percentage of MC are myeloid dendritic cells that express leukocyte markers and have high phagocytic capacity. In the event of MC loss, bone-marrow-derived cells are capable of repopulating the glomerular niche, suggesting a hematopoietic origin of these cells [74]. In this regard, it is likely that increased sympathetic activity may mobilize the bone marrow cells including MC progenitors in hypertensive pathology. Relatively, little is known about MC and their direct role in hypertension. However, it will be of considerable interest to know how these cells contribute to hypertension given their abnormally high proliferative potential in SHR and whether anti-hypertensive and anti-inflammatory treatments would suppress their proliferation.

Vascular remodeling and immunity

Elevated blood pressure is attributable to the resistance of peripheral arteries due to myogenic and structural reduction in lumen diameter. Hypertension is typically accompanied by infiltration of the adventitia and perivascular adipose tissue by macrophages and other inflammatory immune cells. These cells in conjunction with the resident cells of the vessel wall produce cytokines and reactive oxygen species, leading to remodeling of the vessels and surrounding extracellular matrix. Small arteries from patients with essential hypertension undergo remodeling and have a structurally mediated reduction in lumen diameter and increase in media-to-lumen ratio in multiple vascular beds [75]. Vascular remodeling can take place in the absence of increased pressure, but the resulting increase in vascular resistance is a major determinant of hypertension. At the molecular level, remodeling requires dissolution and synthesis of the extracellular matrix proteins. While matrix metalloproteases are known to contribute to dissolution of the matrix, collagen secretion is stimulated for deposition of the matrix.

Multiple cytokines and growth factors are required for this remodeling. Increases in SNA increase adhesion molecules that facilitate trans-capillary migration of immune cells

including monocytes and macrophages. TLRs on both resident cells as well as infiltrating immune cells are activated by DAMPs to synthesize and secrete cytokines [76]. Remodeling of vessels can be inhibited by infusion of liposome-encapsulated clodronate, a bisphosphonate that induces apoptosis and eliminates phagocytic monocytes and macrophages in vivo, suggesting a role of inflammatory cells in the remodeling process [77, 78]. Thus, small artery remodeling and hypertension may represent an underlying inflammatory state. However, it is not understood whether the remodeling is a result of an initial vascular damage, which enhances the migration of the inflammatory immune cells that cause further organ damage.

The cause of the changes in large artery structure and left ventricular mass are likely to be related to the increase in arterial pressure. Adaptation to higher pressure results in reduction of the elasticity of the aortic trunk with an increase in stiffness, which leads to reduced capacity to buffer pulsatile changes in pressure.

Cardiac hypertrophy and hypertension

Cardiac hypertrophy in hypertension may result from the mechanical afterload and the inflammatory response of in situ or migratory immune cells. It is of importance that the two processes, hypertension and cardiac hypertrophy, may be mechanistically uncoupled. In an AngII-induced hypertension model, adoptive transfer of regulatory T cells (Treg cells) reduces infiltration by CD4 + or CD8 + cells in the heart [79]. Cardiac hypertrophy, fibrosis and arrhythmia are reduced. However, these effects are independent of the blood pressure, as adoptive transfer of Treg cells does not reduce hypertension in AngII-infused mice. Whereas Treg cells are known to produce anti-inflammatory cytokine IL-10, the target of Treg cells is not clear. The molecular signaling pathway induced in this model is also not known. In another study, adoptive transfer of Treg cells abolished the increase in macrophage infiltration into the coronary arterioles and the heart of AngII-infused mice [80]. The cardiac hypertrophy with chronic AngII infusion and one following a myocardial infarction (MI) are different as these are mediated by two different inflammatory pathways. Post-MI hypertrophy is dependent on the ubiquitous adaptor protein MyD88 [81], whereas AngII-induced hypertrophy is MyD88-independent (Singh, M.V. and Abboud, F.M. unpublished results). The role of TLRs in hypertension and organ damage is addressed below.

Innate versus adaptive immune system and hypertension

The effect of lymphocytes on the development of hypertension has been studied in greater detail. Activation and expansion of lymphocytes requires the innate immune system. For example, in AngII-induced and DOCA-salt models of hypertension, elimination of monocytes/macrophages or inhibition of their activation attenuates the increase in blood pressure [82, 83].

Complement factors and hypertension-related organ damage

Complement factors are major pro-inflammatory components of the innate immune system. Their serum activity correlates with levels of AngII and systolic blood pressure in humans

[84, 85]. Complement factor C3 induces proliferation in vascular smooth muscle cells (VSMC) of SHR [86]. In addition, VSMCs from hypertensive, double transgenic rats expressing human renin and human angiotensinogen genes, have increased sensitivity to C3 complement fixation [67].

In DOCA-salt rats, increases in leukocyte extravasation and collagen deposits in the ventricular tissue are attenuated after treatment with a complement C5aR antagonist PMX53 (AcPhe-ornithine-Pro-cyclohexylamine-Trp-Arg) without affecting the blood pressure [87]. Thus, C5aR appears to be critically involved in cardiac remodeling in the hypertensive heart. Additional studies are needed to understand the role of the complement system in hypertensive damage and remodeling of tissues and organs.

TLR hypertension and related organ damage

TLR are the best studied integral components of the innate immune system. TLRs are receptors that respond to pathogens and injury through pathogen-associated molecular patterns (PAMPs) and DAMPs. More than a dozen TLRs have been identified in mammals. They function as homo- or heterodimers in defined combinations. TLR-2, TLR-3, TLR-4 and TLR-6 have been reported in the heart and kidney. Despite the remarkable diversity of these receptors in recognizing agonists, all TLRs upon activation induce the NF- κ B transcription factor, leading to expression of pro-inflammatory cytokines and chemokines.

TLR ligands in hypertension

One of the intriguing aspects of the involvement of TLRs in hypertension is the identity of agonists that activate TLR-mediated intracellular signaling. Whereas PAMPs for different TLRs are known, DAMPs are not well characterized. Multiple cell-degradation products, including intracellular proteins such as the high mobility group box 1 (HMGB1) and heat shock proteins, and purines and nucleic acids as well as extracellular matrix components (fibronectin, biglycan, heparin sulfate and hyaluronan), are putative agonists for TLRs [88]. However, the characterization of endogenous ligands of TLR should be considered with caution since TLRs are exquisitely sensitive to exogenous contaminants including LPS, which may cause in false-positive results [88, 89]. In hypertension, it is thought that initial tissue damage by elevated blood pressure releases cellular debris that signals a localized immune response. In genetically predisposed individuals, this initial immune priming may lead to a more potent immune response and additional organ damage and hypertension. Treatment of SHR with TLR4-neutralizing antibody decreases blood pressure [90], suggesting a role for TLR4 in mediating hypertension in this genetic model.

Transcription factors and NF- κ B

Since hypertension is accompanied by inflammation even in the absence of a pathogen, a role of TLRs as sterile injury detectors in hypertension has been proposed. Inhibition of NF- κ B reduces blood pressure and kidney damage in SHR [70]. In double transgenic rats with renin and angiotensinogen over-expression, hypertension is accompanied by extensive infiltration of immune cells and damage to the kidney [91]. Administration of aspirin reduces NF- κ B activation, immune cell infiltration and renal damage. However, blood

pressure is unaffected despite the abrogated organ damage. Conversely, in a helix-loop-helix transcription inhibitor *Id2*^{-/-} mice, AngII-induced hypertension is ameliorated, but end-organ damage is not [92]. Thus, different mechanisms can be responsible for the AngII-induced increase in blood pressure and organ damage.

In addition to the NF- κ B activation, TLRs can also induce other transcription factors, such as AP-1 and interferon-regulatory factors (IRF). IRF3 transcription factor is activated in AngII-infused mice, likely through a MAP kinase pathway [93]. Interestingly, *lrf3*^{-/-} mice develop cardiac hypertrophy upon AngII infusion, but not cardiac fibrosis [93]. Overexpression of IRF4 in mouse heart results in increased cardiac hypertrophy with aortic banding [94] and in *lrf4*^{-/-} mice the cardiac hypertrophy is reduced. This effect is thought to be mediated through activation of CREB.

AngII induces IL-6 production in aortic smooth muscle cells through activation of AT1 receptors and the JAK/STAT pathway [95, 96]. A role of TLR has also been proposed [97, 98]. Yet, how AngII and TLR signaling intersect is not known. In cultured VSMC, AngII-induced TNF- α secretion occurs presumably through a TLR4-mediated mechanism that involves intracellular ERK signaling [99].

Abnormal pro-inflammatory response to TLR activation in SHR

More recently, our laboratory has shown that in SHR and WKY splenocytes, TLR activation and cytokine production can be differentially influenced by nicotine and AngII binding to nACh and AT1 receptors, respectively [63]. Splenocytes from SHR exhibit greater inflammatory responses (cytokine production) than splenocytes from WKY control rats when the cultured cells are stimulated with TLR7/8 or TLR9 ligands in the presence of AngII. A similar enhancement of cytokine production was observed when SHR splenocytes were treated with TLR ligands in the presence of nicotine, an nAChR agonist. This is in contrast with the inhibition of cytokine production by nicotine in the WKY (Fig. 1).

In addition, nicotine also increased the proliferation of a CD161+ cell population in prehypertensive SHR splenocyte cultures. Although CD161 was initially identified as an NK cell marker, it is now known to be expressed on a variety of cells of both the innate and adaptive immune systems [100]. Moreover, CD 161 expression correlates with IL-17 synthesis in Th17 cells [101]. Our preliminary results show that SHR have an abnormally high percentage of CD 161+ cells in the spleen with increased potential for IL-17 synthesis [102], Singh, M.V. and Abboud, FM, unpublished results). These differences in the immune cell populations, cellular proliferation and cytokine production in the SHR suggest that the genetic hypertension in SHR may be caused in part by a dysregulated innate immune response related to AngII and the autonomic cholinergic stimuli.

Selective TLR adaptor proteins in hypertension

We have found that AngII-induced hypertension and the organ damage depend on specific adaptor protein molecules based in the signaling pathway of TLR. Signaling from agonist-bound TLR to intracellular signaling pathways is propagated by 'adaptor proteins.' Five distinct adaptor proteins participate in TLR signaling. Based on the known role of the

adaptor protein MyD88, these signaling pathways are called MyD88-dependent or MyD88-independent. TLR4 has been implicated to play a role in hypertension [90, 98, 103]. TLR4 is unique among TLRs as it signals through both these pathways. We directly tested the role of TLR4 and MyD88 in AngII-induced hypertension in mice. Chronic AngII infusion in WT mice increased blood pressure and induced cardiac hypertrophy. In TLR4-deficient mice, blood pressure was elevated in AngII-infused mice, but cardiac hypertrophy was attenuated. However, AngII-infused MyD88^{-/-} mice displayed both elevated blood pressure and cardiac hypertrophy. Interestingly, MI-induced cardiac hypertrophy was attenuated in MyD88^{-/-} mice [81]. Thus, while the MyD88-dependent pathway contributed to MI-induced cardiac hypertrophy, it does not play a significant role in AngII-induced organ damage. Equally important is the uncoupling of AngII-induced hypertension and cardiac hypertrophy. AngII hypertrophy is TLR4 dependent and MyD88 independent, whereas AngII hypertension is mediated by alternative TLR or adaptor protein. The identification of endogenous ligands activating these pathways would be of interest.

Summary and conclusions

The immune system plays diverse and important roles in hypertension and related end-organ damage. A dysregulated inflammatory immune response affects the CNS and enhances sympathetic nerve activity. This increase in sympathetic activity stimulates the mobilization of hematopoietic stem cells, monocytes and lymphocytes from bone marrow and spleen to the vasculature, heart, kidneys and the CNS where these cells significantly contribute to end-organ damage seen in hypertension. A powerful, parasympathetic, vagal cholinergic and anti-inflammatory pathway is constitutively active that prevents NF-κB activation in immune cells and may be dysregulated in hypertension.

A large body of work has convincingly demonstrated the role of the adaptive immune system and lymphocytes in the pathology of hypertension. However, much less is known about the magnitude of contribution of the innate immune system. Since the innate immune system primes and activates the adaptive immune system, the understanding of its role and the mechanism of its action in hypertension are of great significance.

In the clinically predominant forms of hypertension, it will be necessary to define the role of specific immune cell populations such as monocytes, macrophages, NK cells and Th17 cells in determining the blood pressure and end-organ damage. Cell sorting, selective depletion of cell populations and adoptive transfer can address these issues that will have considerable translational significance. For example, our identification of proliferating immune cells with a CD161 cell marker in prehypertensive SHR may provide novel mechanistic and potentially therapeutic insights.

The role of TLR pathways and their molecular components in hypertension and organ damage need to be identified and characterized in detail. The activation of different TLRs on immune cells by endogenous and exogenous ligands may be sensitized to release harmful cytokines in different models of hypertension. A novel concept that links the autonomic and immune systems is that of modulation of the TLR response by activation of adrenergic, cholinergic and angiotensinergic receptors that are co-expressed on the immune cells (Fig.

1). Activation of adrenergic and angiotensin receptors enhances TLR-mediated pro-inflammatory responses whereas activation of cholinergic $\alpha 7$ -nicotinic receptors suppresses the pro-inflammatory response. We have demonstrated that the AngII-induced enhancement of this response to TLR activation is exaggerated in the prehypertensive SHR. Conversely, the nicotine-induced suppression of the cytokine response is reversed to a pro-inflammatory response in SHR. In addition, the expression of the $\alpha 7$ -nACh receptor is decreased in end organs in several models of hypertension raising the prospect of therapeutic targeting of this response.

Thus, two important conclusions can be drawn: (A) the fatal consequences of sympathetic over-activity and the salutary effect of parasympathetic activity is determined by their powerful regulatory influence on the immune system and (B) in hypertensive disease, the level of arterial pressure elevation and the cardiac hypertrophy or end-organ damage are uncoupled by virtue of their regulation by different immunological pathways.

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Figure 1.