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Review

Microglia, autonomic nervous system, immunity and hypertension: Is there a link?

You Li[a,b], Bo Wei[a], Xiaoli Liu[c], Xiao Z. Shen[d], Peng Shi[a,*]

[a] Department of Cardiology of the Second Affiliated Hospital, and Institute of Translational Medicine, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China
[b] Key Laboratory of Medical Molecular Virology, Shanghai Medical College, Fudan University, China
[c] Department of Neurology, Zhejiang Hospital, Hangzhou, Zhejiang, China
[d] Department of Physiology, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

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ABSTRACT

Hypertension ranks the most common risk factor for cardiovascular diseases, and it affects almost one third of adult population globally. Emerging evidence indicates that immune activation is highly involved in the entire progress of hypertension and end organ damage. In addition to immunity, autonomic nervous system, particularly sympathetic nervous system, is one of the most conserved systems to maintain body homeostasis. Immune and sympathetic activities are found simultaneously increased in hypertension, suggesting a synergistic action of these two systems in the progression of this disease. Microglia, the primary immune cells in the central nervous system, have been suggested in the regulation of sympathetic outflow; depletion of microglia alters neuroinflammation and pressor responses in hypertensive models. In this review, we firstly updated the current understanding on microglial ontogeny and functions in both steady state and diseases. Then we reviewed on the interaction between autonomic nervous system and peripheral immunity in hypertension. Microglia bridge the central and peripheral inflammation via regulating the sympathetic nerve activity in hypertension. Future exploration of the molecular linkage of this pathway may provide novel therapeutic angel for hypertension and related cardiovascular diseases.

1. Introduction

Hypertension affects one-third adult population globally and is the major risk factor for cardiovascular diseases [1], metabolic diseases and neurodegenerative diseases [2–4]. Despite the enormous endeavor of management and decades of research, the prevalence of hypertension continues to be rising. Since the most recent antihypertensive drug, aliskiren, was approved by FDA in 2007, there has no new drug emerged for hypertension in the market over the past 10 years. This may be due to the lack of efficient drug target(s) and the complexity of pathogenesis with multiple organ/tissue involvement. The over driven sympathetic nerve activity (SNA) is one of the hallmarks in hypertension [5,6]. The branches of sympathetic nerves control the tonicity of vasculature; meanwhile SNA also intensively innervates the immune organs such as spleen and bone marrow [7,8]. Of note, both the central and peripheral immune systems have been activated in hypertension [9–12]; thereby the neuro-immune crosstalk amplifies the complexity of investigation of hypertension. Understanding the interactions between the nervous and immune systems would help us understand the mechanism of hypertension development, and may also provide novel targets for the treatment. In this review, we summarize recent advances related to the interactions between microglia-centered central inflammation and the autonomic nervous system, in hypertension, and provide an analytical review of mechanisms that how neural pathways regulate peripheral immunity, which in turn give feedback to the regulation of blood pressure.

1.1. Updates of microglia in ontogeny and function

The CNS is commonly considered to be largely devoid of immune entities with the exception of microglia (a macrophage-like cell). As the resident immune cells in the parenchyma of the CNS, microglia is constituting 5–12% of total glial cells in the mouse brain depending on specific brain regions [13]. The detailed aspects of microglial physiology have been comprehensively reviewed in the past [14–17]. For a long time, the origin of microglia is a puzzle, until the lineage tracing

* Corresponding author at: Department of Cardiology, The Second Affiliated Hospital of Zhejiang University, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China.
E-mail address: ship@zju.edu.cn (P. Shi).

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technique clearly unraveled that microglia are derived from the primitive c-Kit$^+$ erythromyeloid progenitors in the yolk sac around embryonic (E) day 9.5, which definitively demonstrates the independency from the hematopoietic cells (appearance after E16.5) in mouse [18]. However, the maintenance of microglia population is still ambiguous (self-renewal *vs.* migration from the blood-bored myeloid cells) in homeostatic conditions and in diseases [19,20]. Regardless this issue, it is well studied that both colony stimulating factor 1 receptor (CSF1R) and transforming growth factor (TGF) β receptors are required for the development and maintenance of microglia population and identity [21–23]. Using the deep RNA sequencing, the signature gene panels in microglia are identified: homeostatic genes including Tmem119, P2ry12, Tgfbr1, siglech and Sall1, and disease-associated genes such as Spp1, Gpnmb, Igf1, Clec7a, Lpl, Cd9, Cd63, Lgals3, Fabp5, Apoe and Tyrobp [24,25]. Although the featured gene panels are identified by RNA sequencing, the mechanisms how these genes (*e.g.* Apoe) regulate microglial function and mediates microglia-neuronal communication are still unclear. In addition, while the markers for discriminating distinctive subtypes of T cells have been well established, explicit markers to differentiate microglial activation statuses have not been defined.

Although the mystery of microglial ontogeny has been solved, one interesting finding is that the repopulated microglia-like cells from the hematopoietic myeloid cells adopt microglial transcriptome profile, suggesting the brain imprint to immune cells [20]. As the professional phagocytes in the CNS, microglia are of importance in maintaining brain homeostasis *via* constantly patrolling and engulfing debris or pathogens. With an expanded function, microglia sustain neurogenesis *via* phagocytosis both in the early-stage development and in the adulthood as summarized in Fig. 1. In the early stage of life, amoeboid microglia trigger programmed cell death [26,27] and phagocytose apoptotic neurons [28,29], thereby microglia regulate neuronal numbers and rewire the network [30]. In adult brains, microglia actively survey and shape neuronal circuits *via* synaptic pruning, which eliminates excess synapses and/or strengthening functional synapses [31,32].

Like macrophages in the peripheral organs, microglia are not a homogenous population. Microglia heterogeneity could be characterized by production of bioactive molecules and transcriptome profiles [33,34]. This could be due to the imprints of region-specific environment [24,35–38]. For instance, microglia in subventricular zone regulate neurogenesis *via* specifically releasing factors such as TGFβ, tumor necrosis factor (TNF) α, insulin-like growth factor (IGF) 1 and toll-like receptor (TLR) 9 [39,40]. Using single-cell RNA sequencing, microglia can be grouped into seven clusters [24]. One cluster of microglia exclusively distributes within the high proliferation regions (corpus callosum and cerebellar white matter) in the early postnatal stage, suggesting they may contribute to the gliogenesis. More intriguingly, these microglia highly expressed Clec7a (also known as Dectin 1), which is a damage-associated molecule (DAM) in Alzheimer's disease (AD) [25,41,42]. The regional differences in microglial phenotypes may result in variable exposure of neurons to microglia-derived factors *e.g.* inflammatory mediators and trophic signaling, which could impact dendritic spine formation/elimination and synaptic strengthen [43].

In addition to the immune-related molecules, microglia express multiple neurotransmitter receptors including glutamate-, GABA-, adrenergic-, adenosine-receptors [44]. This potentiates the microglial responses to neuronal activity. It is shown that glutamate triggers TNFα release from cultured microglia; and this response is blocked by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor [45]. Thus, the neurotransmitter receptors may facilitate the transition of microglia from an immunosuppressive into an inflammatory state in disease conditions.

In addition to microglia, bone-marrow derived macrophages in CNS also contribute to CNS immune stability [46]. Perivascular macrophages (PVM) are named from their proximity to cerebral blood vessels. Although sharing a lot of similarities with parenchyma microglia, PVM have different ontogeny and display a different marker panel including MHC-II, H2-Ab1 and CD74 [24]. PVM and circulating hematopoietic myeloid cells also contribute to the immune responses during CNS infection. More importantly, they may serve as a reservoir of microglia after microglial depletion and under pathological conditions, although this topic is still under debating as mentioned above [19,20,47–50]. Recent work by Harris et al. showed that depletion microglia in adult

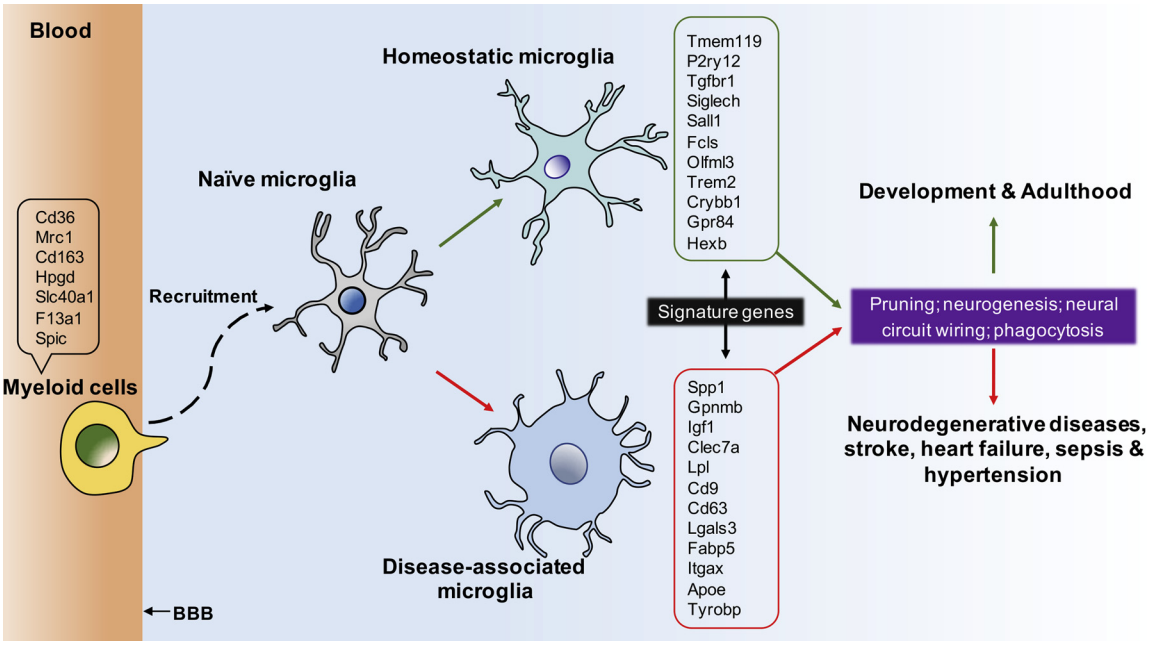

Fig. 1. Microglia in different activation states regulate neuronal function. Microglia are programed into homeostatic or disease-associated condition by local cues. Activated microglia are classified into homeostatic and disease-associated microglia characterized by different transcriptomic profiles. Microglia in different status regulate neuronal activities by synaptic pruninging, neurogenesis, neural circuit wiring and phagocytosis in normal or diseases. Blood-bored myeloid cells with a unique gene profile engraft into the brain parenchyma as a supplemental pool to maintain microglia homeostasis.

mouse brain resulted in approximately 95% repopulation from the bone marrow-derived myeloid cells [51]. Interestingly, those monocytes-derived cells adopted microglial signatures at transcriptional, epigenetic and functional aspects after residency in the brain parenchyma [20]. Overall, the bone-marrow-derived myeloid cells could be the second tie of pool for the maintenance of microglial homeostasis.

1.2. Neuroinflammation and sympathetic nerve activity

Hypertension is characterized by two prominent features in terms of neural etiology: elevated SNA and neuroinflammation [6,11,52]. About 50% patients with essential hypertension are observed with enhanced SNA [53,54]. Additionally, SNA is dramatically increased in various experimental hypertensive animal models such as angiotensin (Ang) II-, deoxycorticosterone acetate (DOCA)-salt and genetic hypertensive (spontaneous hypertension rat [SHR]; double transgenic mouse expressing human renin and human angiotensinogen, and Goldblatt (two kidneys; one clip; 2K1C) hypertensive models [23,55–59]. Substantial evidence indicates that neuroinflammation, tightly associated with hypertension, contributes to elevated sympathetic drive [60,61]. Administration of IL-1β into PVN region *via* intracerebroventricular (ICV) infusion remarkably enhanced SNA and blood pressure (BP) [62]. In contrast, central delivery of anti-inflammatory reagents, such as IL-10 or minocycline suppressed SNA and the elevated BP in hypertensive animal model [61]. Thus, neuroinflammation is a key factor that drives SNA and exacerbates hypertension. Interestingly, it has been reported that the macrophage migration inhibitory factor (MIF), an immunoregulatory mediator, serves as a negative regulator of Ang II signaling in hypertension [44,63,64]. MIF exerts its antagonizing effects on AT1 receptor *via* its intrinsic thiol-protein oxidoreductase activity, which results in the scavenging reactive oxygen species (ROS) [44]. This work suggests that some immune mediators have direct effects on neuronal activity.

Recent studies underlie an important role of microglia in neuroinflammation and blood pressure regulation [62,65–69]. During hypertension, microglia are activated by hypertensive stimuli (*e.g.* Ang II) [66] and release multiple proinflammatory cytokines such as TNFα, IL-1β, IL-6 and anti-inflammatory cytokines *e.g.* IL-10 [68,70]. Consistently, inhibition of central Ang II signaling resulted in attenuated neuroinflammation [71,72] and restored blood pressure [73]. Activated microglia exhibit morphological and phenotypic changes [61,65]. Both depletion of activated microglia [68] or pharmacological inhibition of microglia [65] reduced neuroinflammation and alleviated hypertension. These observations strongly support the idea that microglia participate in the regulation of neuroinflammation and blood pressure. Another interesting finding is that microglia activation results in an increase in glutamate receptor expression on neurons, suggesting that activated microglia could modulate neuronal plasticity [68]. These studies imply that alteration of microglia activation status could directly affect neuronal activation [74,75].

As mentioned above, after hypertension is established, activated microglia promotes neuroinflammation and exacerbates hypertension [65,68]. However, in steady state, microglia stay in a rather immunosuppressive state [76]. Our work identified that TGFβ is constitutively expressed in CNS and is a determinant in microglia phenotypic fate and central BP regulation [69]. Depletion of central TGFβ induced elevated neuroinflammation and exacerbated hypertension. Supplementing TGFβ *via* ICV infusion reduced microglia activation and prevented Ang II induced hypertension. Moreover, using microglia depletion and adoptive transfer strategies, we found that TGFβ modulated BP by suppression of microglia activation. Consistent with our finding, intracranial administration of TGFβ improved the recovery from hemorrhagic stroke *via* inhibition of microglial activation [77]; targeted deletion of TGFβ receptor on microglia promoted rapid differentiation of quiescent microglia towards an inflammatory state [78]. Collectively, we concept that microglia-induced neuroinflammation contributes to hypertension development, whereas TGFβ as a key homeostatic factor, suppresses hypertension by modulating microglia activation. In the hypertensive state, how microglia contribute to the regulation of pre-sympathetic neurons such as those in the PVN is unclear so far. Further studies are needed to investigate whether microglia regulate autonomic neuronal activity by direct action (*e.g.* synaptic pruning), or indirect effects (*e.g.* release of ROS or cytokines) as reported in the other neurons [79,80].

Besides microglia, brain PVMs may also participate in neuroinflammation and hypertension development. Depletion of brain PVMs *via* ICV administration of clodronate liposomes reduced TNFα-elicited increase in renal SNA and BP, and attenuated neuroinflammation as well as sympathetic outflow in a myocardial infarction animal model [81]. Recently, the study from Faraco et al. reported that activated PVMs by blood borne Ang II increased ROS *via* upregulation of Nox2, which in turn disrupted the integrity of blood brain barrier (BBB) and resulted in cognitive dysfunction [82]. This finding was echoed by another study which showed that hypertension resulted in BBB leakage, which permits the entry of circulating Ang II into the brain parenchyma [83]. Collectively, PVMs could participate in the modulation of neuronal function *via* maintenance of BBB integrity in hypertension, which underlies the dysfunction of BBB in hypertension.

1.3. Splenic sympathetic nerve activity and immune activation

Pioneering work identified the interaction between neural circuitry and immune responses [84,85]. Sympathetic noradrenergic nerve fibers are highly distributed in the immune organs, including thymus, spleen, lymph nodes and bone marrow [86]. Spleen, the largest lymphatic organ, regulates immune responses. Splenic nerve, the efferent sympathetic nerve, stems from celiac-mesenteric plexus; the latter comes from the sympathetic ganglionic chain [86]. Consistently, adrenergic receptors such as α and β are highly expressed in a variety of immune cells (macrophage, monocyte, neutrophil and T cells). The long-holding concept is that autonomic (both sympathetic and vagus) nerve activation exerts immune suppression [84,87–89]. For example, activation of adrenergic β2 receptor inhibits chemokine receptor-mediated T lymphoid cells egression [89]. Immune suppression induced by sympathetic activation has protective effects in severe inflammation conditions *e.g.* stroke and sepsis [90,91]. However, current evidence suggests that in hypertension, elevated autonomic signals aggravate immune activation. For instance, increased splenic nerve activity induced by ICV infusion of Ang II up-regulated an array of proinflammatory cytokines at mRNA level in the splenocytes [92]; another study demonstrated that increased splenic placental growth factor (PlGF) triggered by sympathetic activation resulted in T cell activation and egression toward aorta and kidney, which permitted the onset of hypertension [93]. Notably, additional work from the same group indicated that parasympathetic vagus nerve facilitated sympathetic-driven immune responses in hypertension [94].

These contradictory observations about the effects of autonomic activity on the peripheral immune responses may reflect the fact that unlike stroke and sepsis, hypertension is a chronic low-grade inflammatory condition. Their initiating insults are very different. Tracey's group found that stimulation of afferent vagus nerve fibers with endotoxin or proinflammatory cytokines in stroke resulted in the activation of hypothalamic-pituitary-adrenal anti-inflammatory responses [95]. Electronic stimulation of efferent vagus nerve inhibits the release of proinflammatory cytokines such as TNFα. Thereby, they describe the neuroimmune interaction as "inflammatory reflex", centered by the activation of parasympathetic nerve activity [84]. In hypertension, the immune system is activated by a mild but persistent exposure to the stressed tissues such as endothelial cells due to the hemodynamic disturbance [6]. Increased shear stress is reported to irritate red blood cells and vascular endothelial cells which in turn release ATP [96]. As a molecule of damage-associated molecular patterns

(DAMPs), increased extracellular ATP mobilizes and activates the immune cells, such as monocytes and dendritic cells, through P2 receptors [97–99]. In such a situation, the autonomic nervous systems may respond with different neural circuits accordingly, which requires further investigation.

1.4. Renal sympathetic nerve activity and immune activation

In hypertension, the most well studied organ of sympathetic innervation is the kidney. Recent studies unravel that renal SNA activation contributes to renal immune activity in addition to the tonicity of renal vasculature [100]. It has been reported that renal denervation (RDN) prevents dendritic cell activation in kidney and subsequent T cell infiltration to the kidney and aorta. As a consequence, RDN prevents end-organ damage and Ang II-induced hypertension [100]. It was found that vascular cell adhesion molecule (VCAM) 1 serves as an antigen to activate and recruit immune cells in hypertension [100], and the expression of renal VCAM-1 was significantly decreased after RDN. Meanwhile, sympathetic nerve also enhances the activity of renin-angiotensin system in the kidney. Recent study from Giani's group shows that angiotensin converting enzyme (ACE) in the kidney exacerbates renal fibrosis and inflammation [101], which is mediated by the catalytic N-domains of ACE in diabetic kidney disease [102]. Whether renal sympathetic nerve activity mediates the ACE activation need further investigation. In chronicle order, sympathetic overexcitation has been shown to occur prior to the onset of the hypertension, indicating SNA overactivation is persistent throughout the entire hypertension development [6].

1.5. Sympathetic nerve activity and bone marrow

Ample evidence indicates that immune cells including monocytes and dendritic cells constitute an immune etiology of hypertension [9,103,104]. Of note, both of these immune cells are stemmed from the bone marrow, prompting bone marrow an investigating interest of hypertension. Bone marrow is intensively innervated by sympathetic nerves, mainly adrenergic nerve fibers [7]. Adoptive transfer of normotensive Wistar Kyoto rat (WKY) bone marrow into the SHR reduced arterial blood pressure, SNA and neuroinflammation [105]. This result may be achieved by which the normalized peripheral immune state lowers the CNS stimulation on microglial activation and SNA excitation, suggesting an intriguing linkage of central and peripheral immunities. Bone marrow cells highly express adrenergic receptors. The chimeric mice receiving β_1- and β_2-dificient bone marrow displayed a lower baseline BP and decreased circulating immune cells [106], which suggests another direct interaction between sympathetic nerve system and the immune system. Consistently, Zubcevic et al. showed an elevated sympathetic input to the bone marrow, evidenced by an increased norepinephrine level in the bone marrow of SHR [107]. Elevated SNA increased inflammatory cells in both bone marrow and circulation, meanwhile decreased circulating endothelial progenitor cells (EPC) [107]. EPC are the primary precursor cells of vascular endothelial cells and could replace the damaged endothelium in hypertension [96]. This study strongly suggests exacerbated inflammation and impaired vascular repair *via* over-drive of sympathetic outflow. In contrast, pharmacological blockade or genetic knockout of adrenergic receptors in the bone marrow cells suppress egression of hematopoietic cells [7,108]. Over activation of renin-angiotensin system could be an alternative mechanism in hypertension. Kim et al. show that Ang II had direct effect on promoting proliferation, differentiation and egression of hematopoietic bone marrow cells [109]; as a return, these hematopoietic cells contribute to the peripheral inflammation and exacerbate hypertension. Future studies are needed to investigate whether the activation of immune cells by Ang II is a direct or sympathetic-mediated secondary effect; and whether there is a differential effect of sympathetic input on different subtypes of bone marrow cells.

1.6. Crosstalk of immunity and sympathetic nerve activity in hypertension

Hypertension, by nature, is a hemodynamic perturbation, which is the product of increased cardiac output and/or increased systemic vascular resistance. The major damage elicited by chronic blood pressure increase is vascular fibrosis and sclerosis [97], a process that inflammatory cells are actively involved in. The roles of inflammatory cells in the vessel pathogenesis have been further demonstrated by the observations that mice either lack of T cells or depleted with macrophages developed much milder aorta fibrosis after hypertension induction [119,120]. This is also true for cerebral vasculature but with more complications. Besides arteriole sclerosis, hypertension induces leakage of BBB [82]. Interestingly, leaky BBB renders the access of blood-bored substances, *e.g.* fibrinogen and low-density lipoprotein, into the brain parenchyma and activate microglia [79,80]. Activated microglia orchestrate neuroinflammation and, in turn, deteriorate the damage of central vasculature [114,115]. This cycle of BBB leakage, microglia activation and central vasculature damage share a lot of similarities between hypertension and aging, suggesting a common pathway of microglia/vessel-mediated dysfunction in hypertension and cognitive diseases. Vascular endothelial cells, lining alone the lumen of the blood vessels, play an important role in the regulation of vascular tone. During hypertension endothelial cells display impaired function with decreased nitric oxide production and regenerative ability [110]. Meanwhile, hypertension increases the expression of adhesive molecules *e.g.* VCAM1 in the endothelium, which allows the access of peripheral immune cells into the brain parenchyma [111]. Interestingly, endothelial cells are activated characterized by the upregulation of genes associated with cell adhesion, inflammation, stress response and vascular remodeling at transcriptional level in aged mouse brain, consistent with hypertensive state [112]. Elevated VCAM1 in aged endothelial cells induced microglial activation; and blocking VCAM1 restored microglial status [112]. This suggests a potential interface between brain and peripheral immunities at the cerebrovascular unit. As mentioned earlier, hypertension causes the leakage of the BBB [82], which renders the access of blood-derived factors into the parenchyma to induce microglial activation [113]. Activated microglia promote dendrite and spine elimination in hippocampal neurons *via* release of ROS [80]. In DOCA-salt hypertensive model, microglia are recruited to the endothelium of the cerebral vasculature prior to the onset of hypertension [58]. As a return, these perivascular microglia may disrupt vascular integrity [114,115], which further aggravates microglial activation.

Inhibition of central immune activation at the early stage of hypertension achieves a significant depressor response, which results from a halt to SNA overdrive [116,117]. The latter aggravates peripheral inflammation and accelerates hypertension development. To make a hypothetic picture, blood bored signals or brain-derived local cues may induce microglial activation in hypertensive condition. Activated microglia modulate autonomic neuronal activity in the hypothalamic and brainstem nuclei (*e.g.* PVN, RVLM, NTS and DMN). Altered sympathetic and/or parasympathetic nerves innervates to the immune organs/tissues, vasculature and kidney, which result in the hypertension symptoms *e.g.* inflammation, vasoconstriction and renal dysfunction. Hypertension-induced systemic inflammation may further inflame microglia in the CNS and enhance SNA, which aggravates hypertension. This hypothesis is schematically pictured in Fig. 2. Inflammation elicited by transient increase in arterial pressure is an initial trigger to drive this vicious cycle in the early stage of hypertension, and then elevated SNA becomes the major player in maintaining the prolonged hypertension. Thereby inhibition of renal SNA such as RDN, instead of anti-inflammation, achieves many successes in the treatment of resistant hypertension [100]. To break the vicious cycle, targeting the sympathetic regulatory factors *e.g.* microglia would be a potential therapeutic window [118]. By checking microglial status, it could maintain BBB integrity and restore autonomic neuronal activity,

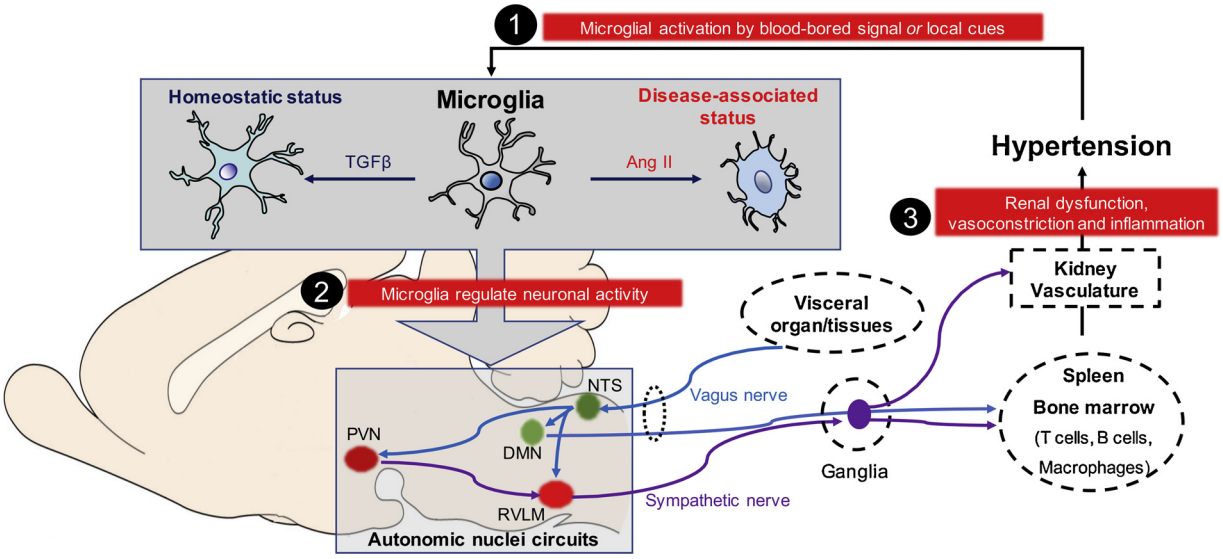

Fig. 2. Hypothetic mechanism of microglia-mediated regulation of autonomic function in hypertension. Schematic illustration showing microglia switching from homeostatic to disease-associated states in response to blood-bored signals or brain-derived stimuli in normotension and hypertension in step 1. Activated microglia regulate autonomic neuronal activity in the hypothalamic PVN and brainstem NTS, DMN and RVLM nuclei in step 2. Sympathetic and parasympathetic vagus nerves innervate peripheral immune tissues/organs, kidney and vasculature to promote renal dysfunction, systemic vasoconstriction and inflammation, which further aggravates hypertension in step 3.

thereby lower sympathetic outflow and blood pressure.

2. Conclusion

In this review, we focus on the neural-immune communication and describe a hypothetic pathway in which hypertension induced neuroinflammation increases the sympathetic nerve activity that drive splenic, renal or bone marrow nerve activation and regulates peripheral immune response, in turn, exaggerates hypertension. Both central and peripheral immune systems contribute to the inflammatory status, and autonomic nervous system particularly sympathetic nervous system orchestrate all the organs together in hypertension development. To break the vicious cycle of hypertension-inflammation, future studies may explore the mechanisms by which autonomic nerve activity is modulated in hypertension.

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Declaration of Competing Interest

N/A.

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