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Dysfunctional brain-bone marrow communication: A paradigm shift in the pathophysiology of hypertension

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Abstract

It is widely accepted that the pathophysiology of hypertension involves autonomic nervous system dysfunction, as well as a multitude of immune responses. However, the close interplay of these systems in the development and establishment of high blood pressure and its associated pathophysiology remains elusive and is the subject of extensive investigation. It has been proposed that an imbalance of the neuro-immune systems is a result of an enhancement of the "pro-inflammatory sympathetic" arm in conjunction with dampening of the "anti-inflammatory parasympathetic" arm of the autonomic nervous system. In addition to the neuronal modulation of the immune system, it is proposed that key inflammatory responses are relayed back to the central nervous system and alter the neuronal communication to the periphery. The overall objective of this review is to critically discuss recent advances in the understanding of autonomic immune modulation, and propose a unifying hypothesis underlying the mechanisms leading to the development and maintenance of hypertension, with particular emphasis on the bone marrow, as it is a crucial meeting point for neural, immune, and vascular networks.

Keywords

Inflammation; Autonomic nervous system; ANS; Immune system; IS; Microglia; Neuroimmune modulation; Bone marrow; Vagal immune reflex; Hypertension; Cardiovascular disease; CVD

1. Introduction

Hypertension remains a global health concern despite significant advancements in its treatment in recent years. Approximately 10% of hypertensive patients suffer from resistant hypertension [1, 2], characterized by blood pressures that remain uncontrolled in spite of simultaneous administration of three antihypertensive agents of different classes [3]. The neurogenic component of resistant hypertension presents with a dysfunctional autonomic nervous system (ANS) [4-8], increased norepinephrine (NE) spillover and sympathetic nerve activity (SNA) and decreased cardiac parasympathetic tone [9-16]. Similar findings have been described in association with several of the hypertension comorbidities, including

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Compliance with Ethics Guidelines

Conflict of Interest

Monica M. Santisteban, Jasenka Zubcevic, David M. Baekey, and Mohan K. Raizada declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

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obesity, diabetes, and sleep apnea [17-20], thus complicating diagnosis and treatment [3, 21].

Multiple emerging therapies target autonomic dysfunction in patients with neurogenic hypertension [4, 8, 22, 23]. Renal denervation therapy [24-28] employs radiofrequency to specifically ablate the renal sympathetic nerves [22] resulting in a significant and long-lasting decrease in blood pressure and whole-body norepinephrine spillover in some patients [29-32]. While proof of concept has been established, the long term effectiveness of this strategy remains to be validated in view of recent evidence of reinnervation of the kidney following ablation [33]. Renal denervation may only be effective in lowering blood pressure and muscle sympathetic nerve activity in a small proportion of patients [34], possibly owing to low renin levels in some cases of neurogenic hypertension [35], amongst other issues. Similarly, chronic carotid baroreceptor activation has been shown to lower blood pressure and sympathetic activity in resistant patients [36-39], prompting initiation of clinical trials with promising long term results [40, 39]. Other more adventurous techniques such as the deep brain stimulation [41-47] and surgical relief of micro-vascular compression [48, 49] have demonstrated promising outcomes, but the invasive nature of these procedures decreases their general therapeutic use and renders them mainly experimental.

Present therapies that target the neurogenic component of hypertension highlight the need for novel therapeutic strategies for patients with resistant hypertension. However, the invasive nature of the procedures and the potential high cost and relatively low efficacy of treatment, coupled with a lack of understanding of underlying pathophysiological mechanisms of autonomic imbalance, further complicate the development of innovative strategies for the treatment of resistant hypertension. Recent advances have underscored the role of the immune system (IS) and the importance of neuro-immune pathways in autonomic regulation in hypertensive patients and animal models of hypertension. The aim of this review is to summarize latest advances in the field, review the current understanding of connections between the autonomic and immune systems, and discuss issues that remain to be addressed in the field of autonomic modulation of immunity in hypertension.

2. Immune system and neurogenic hypertension

It is well established that hypertension and cardiovascular disease (CVD) in humans are characterized by increased systemic inflammation [50-54]. Increased circulating levels of inflammatory markers have been reported even in pre-hypertensive patients [55-57], suggesting a causative role of the immune system in CVD. As a result, extensive investigation is underway to elucidate the role of innate and adaptive immunity in the development and maintenance of hypertension. Animal experiments have demonstrated that elimination of the immune response by thymus transplant or immunosuppressant drugs can delay and even arrest the progression of hypertension [58, 59]. David Harrison's group was among the first to show that T-lymphocytes are essential for the development of hypertension in several animal models [60, 61]. For example, RAG-/- mice lacking the mature B- and T-lymphocytes did not develop high blood pressure, but the adoptive transfer of T-cells, not B-cells, was able to restore the hypertensive phenotype [60, 61], suggesting an exclusive role of activated T-cells in hypertension. It is pertinent to note that not all types of T-cells behave similarly, as recent reports showed that the adoptive transfer of the T regulatory (Treg) lymphocytes (CD4+/CD25+), but not the T effector (helper) lymphocytes (Th, CD4+/CD25-), prevented both the angiotensin II (Ang II)- and aldosterone-dependent hypertension [62, 63]. Treg lymphocytes are thought to be able to suppress both the innate and adaptive immune responses by suppressing the pro-inflammatory actions of the effector Th lymphocytes, thereby playing a role in immune system homeostasis. These and other studies have led to the hypothesis that activation of the IS in hypertension depends on

formation of specific neoantigens, which, through dendritic cell (DC)–dependent activation, lead to activation of naïve T-cells and their differentiation into effector Th lymphocytes [64]. Thus, Treg lymphocytes are able to protect against the development of hypertension by counter-acting renal vascular remodeling that is induced by effector Th cell activation [64]. However, the triggering mechanism that initiates this process remains to be identified.

Recent animal data suggest that, in addition to the increased pro-inflammatory pathways, anti-inflammatory pathways are dysfunctional in hypertension [65-67]. Francois Abboud's group has recently shown that the anti-inflammatory modulation of the innate IS in normotensive rats is reversed in pre-hypertensive SHRs [67]. They demonstrated that nicotine, a neurotransmitter of the cholinergic neurons, exerted an anti-inflammatory effect by suppressing a large population of myeloid DCs in the WKY, but had an opposite, pro-inflammatory effect in the SHR, exhibited in the activation of macrophages [67]. In another animal model, chronic vascular risk factors have been associated with decreases in cholinergic neurons [68]. Further evidence from a two-kidney one-clip hypertension model suggests that secondary hypertension induces cholinergic receptor down-regulation, which may ultimately contribute to the inflammatory processes [69]. Therefore, the importance of understanding the mechanism of the cholinergic anti-inflammatory pathway in hypertension is becoming increasing evident, and may provide a novel therapeutic target in the treatment of neurogenic hypertension. These pathways will be discussed in the section on autonomic regulation of the immune system.

3. Neuroinflammation and microglia

Involvement of brain inflammation in various CNS diseases such as Parkinson's and Alzheimer's disease and stroke has been well documented [70-72]. However, the role of brain inflammation in hypertension and CVD is less well understood and is a rapidly emerging field. It has been shown that increased inflammation in the cardioregulatory areas of the brain is associated with increased sympathetic nervous system activity and hypertension, and inhibition of inflammation in these brain regions attenuates the hypertension [73-78]. Furthermore, inhibition of pro-inflammatory oxidative stress by specific deletion of $p22^{phox}$ in the subfornical organ (SFO) attenuates hypertension and eliminates vascular inflammation in the chronic Ang II infusion model [74]. In addition, SHRs exhibit increased leukotriene B4 in the nucleus of tractus solitarius (NTS), which has been proposed to be pro-hypertensive in the SHR [79]. Pro-inflammatory pathways, such as NF-κB in the paraventricular nucleus of the hypothalamus (PVN) have been shown to enhance the hypertensive response to Ang II [80]. Taken together, these observations suggest that neuroinflammation plays an important role in the development and maintenance of hypertension.

Increased activity of the renin-angiotensin system (RAS) in hypertensive models [81-83] has a role in driving pro-inflammatory responses in the periphery as well as the brain [80, 84, 85]. For example, chronic knockdown of AT1 receptors in the NTS of SHR animals increases peripheral inflammation and vascular dysfunction [86]. As mentioned earlier, T-lymphocytes are essential for the development of hypertension [60, 61], and central Ang II appears critical for T-lymphocyte activation [87]. A study by Marvar *et al.* showed that lesioning the anteroventral third cerebral ventricle (AV3V) eliminates the Ang II-induced blood pressure increase, T-cell activation, and vascular leukocyte infiltration. The authors postulated a feed-forward mechanism that includes modest increases in blood pressure promoting inflammation, further raising blood pressure, and eventually culminating in severe hypertension [87]. These studies emphasize the link between the central RAS and the immune system. Whether the initial pro-inflammatory trigger comes from the brain remains the topic of many studies, and will be discussed in detail in the following sections.

Investigation of the role of microglia and neuroinflammation in hypertension may provide valuable insight into this problem. Microglia are the immune cells of the central nervous system and make up approximately 12% of the brain cell population [88, 72]. Within the healthy CNS, microglia are tightly regulated in order to continuously monitor the brain environment [89, 90]. Their phenotype can rapidly change in response to alterations of homeostasis, pathological insults, and even systemic inflammation in an attempt to repair injury at inflammatory sites [88, 91, 92]. However, over-activation of microglia is detrimental, as they release pro-inflammatory cytokines and generate ROS, thereby contributing to the inflammation in the brain [77, 76, 93]. Neurogenic hypertension involves activation of microglia in the PVN in both the Ang II-dependent and SHR models [94, 77]. Moreover, close interactions between the microglia, astrocytes, and neurons can lead to the modulation of neuronal activity in the PVN, enhancing the neuronal response to Ang II [95]. On the other hand, inhibition of the brain mitochondrial ROS, but not the peripheral ROS, is able to attenuate hypertension, inhibit microglial activation in the PVN, and normalize peripheral IC levels [78]. Therefore, microglia are emerging as a novel therapeutic target for the treatment of resistant hypertension, although further understanding of the molecular mechanisms underlying these processes is needed.

Taking all this into consideration, we propose that activation of endogenous microglia in cardioregulatory areas of the brain is an *early event* in the development of hypertension (Fig. 1). Ang II and other pro-hypertensive stimuli directly activate the microglia and stimulate the microglial release of the pro-inflammatory cytokines. These cytokines, in addition to the pro-hypertensive stimuli, may influence neuronal activity, particularly in the autonomic areas of the brain (Fig. 1). These central responses then give rise to *intermediate effects* in the periphery, which include autonomic dysregulation, increased inflammation and vascular dysfunction. Furthermore, we propose that the maintenance of hypertension involves a *late event*, in which bone marrow-derived inflammatory progenitors extravasate in brain and differentiate into microglia, further enhancing neuroinflammation in the autonomic areas of the brain. Our model highlights the importance of central pro-hypertensive stimuli, proposing that these processes are crucial for the development of hypertension. Furthermore, we make the novel inclusion of bone marrow sensory inputs which may signal important information about the inflammatory status of the periphery. The role of autonomic dysregulation in the control of inflammatory responses in hypertension will be discussed in the following section.

4. Autonomic regulation of the immune system

The concept that the central nervous system (CNS) can regulate the IS has existed for several decades. However, the notion that heightened emotional stress can exacerbate inflammatory responses has only recently been supported by scientific evidence [96-99]. It is now known that specific cell types such as lymphocytes, myeloid cells and endothelial cells respond to changes in hormones and neurotransmitters of CNS origin [100]. Specifically, activation of the sympathetic arm of the ANS has been shown to play a major role in regulation of inflammatory responses [101]. This is particularly manifested in CVD and diabetes, where a direct link between elevated sympathetic drive and exaggerated inflammation has been demonstrated [50, 78, 102]. In SHR, the pro-inflammatory innate immune response is exaggerated even before the development of the high blood pressure [67], due to elevated central sympathetic drive preceding the blood pressure increase [103]. Furthermore, specific T-lymphocyte responses are crucial in development of Ang II hypertension [61], which is characterized by elevated central sympathetic drive to the spleen [104] and the bone marrow [78], where it directly regulates the activity of pro-inflammatory and other hematopoietic cells [105, 78, 106].

We have recently demonstrated that the chronic Ang II-dependent increase in central sympathetic drive stimulates the release of bone marrow-derived pro-inflammatory lymphocytes. This effect was abolished by blockade of the Ang II effect on the brain, particularly in the PVN [78]. Furthermore, our anatomical tracing studies revealed that the brain-bone marrow connections involve a direct sympathetic neuronal input to the bone marrow, which is enhanced in hypertension [78]. This enhanced ANS-IS communication is also present in other forms of CVD, such as myocardial infarction (MI), where elevated SNS is a major signal for recruitment of hematopoietic cells from the bone marrow [107]. Further, the abundance of adrenergic receptors in metabolic tissues such as fat supports a role for elevated SNS-dependent initiation of inflammatory responses [108-110] in diseases such as diabetes and obesity [61]. The role of SNS is further highlighted by the observation that the release of hematopoietic progenitor cells from the bone marrow depended on circadian oscillations of expression of certain clock genes which were governed by adrenergic stimulation from the sympathetic nerves innervating the bone marrow [111, 112]. Furthermore, blood leukocyte numbers exhibit circadian oscillations [113, 101], with their peak activation and migration from the bone marrow occurring at night [101], corresponding to the highest sympathetic drive in mice. This effect is completely dependent on the presence of the bone marrow sympathetic innervation, as well as the presence of beta 2 and 3 adrenergic receptors on the bone marrow hematopoietic cells, including the EPCs [101]. Since the circadian rhythms are entrained by the suprachiasmatic hypothalamic nuclei [114-116], any changes in neuronal activity within the hypothalamus, such as those seen in neurogenic hypertension [78, 77, 95], may affect the circadian control of the bone marrow activity.

Epidemiological evidence also suggests that these diurnal oscillations are clinically significant. Some inflammatory and immune diseases present a diurnal pattern of onset and progression [117]. For example, in models of sickle cell anemia and septic shock, where increased leukocyte inflammatory response contributes to the pathology of the disease, survival was appreciably compromised when inflammation was stimulated at night compared to the day [101]. In patients with MI, there is a significant increase in onset in the morning (9 am) compared to night (11pm), which is reduced in those receiving beta adrenergic blockers [118]. The diurnal oscillatory pattern of hematopoietic progenitor and immune cell regulation should also be considered when designing bone marrow and organ transplant protocols [112], as evidence suggests differential survival rates of recipients depending on the time of the day of the transplant [101]. In summary, it appears that the SNS plays a pivotal role in regulation of inflammatory responses in health and disease, and that the bone marrow may be a major if not the main contributor to the immune cell pool.

The balancing arm of the sympathetic influence is the parasympathetic arm of the ANS which regulates the “cholinergic anti-inflammatory pathway” or the “vagal immune reflex” [52, 94, 119-121]. Substantial evidence exists supporting the beneficial anti-inflammatory effect of vagal activation in inflammatory and immune conditions [122-128]. Vagal nerve stimulation is effective in reducing the peripheral release of cytokines such as TNF-alpha, IL-6, and IL-1, which is dependent on acetylcholine (ACh)-mediated reduction of macrophage activation via nicotinic acetylcholine receptor (nAChR)-dependent inhibition of NF-κB signaling in these cells [119, 129]. The afferent vagal fibers are also able to sense changes in the peripheral inflammatory status; for example, the glomus cells located in close proximity to the vagal nerve fibers possess IL-1beta binding sites, and therefore the sensory portion of the inflammatory reflex is able to sense changes in IL-1beta levels in the periphery [130]. The sensory message is then relayed to the brainstem, particularly the NTS and the dorsal vagal motor nucleus, where the signal is processed, integrated and relayed back to the periphery via the vagal efferents [121, 131].

It has been proposed that the spleen serves as an end-organ of the cholinergic anti-inflammatory pathway, albeit indirectly [132], as the vagal parasympathetic efferents communicate with the splenic postganglionic nerves via the celiac-superior mesenteric plexus [133, 134]. Therefore, the cholinergic anti-inflammatory vagal-splenic reflex requires activation of the splenic sympathetic (catecholaminergic) postganglionic nerves and possibly release of NE. This reflex could exert its anti-inflammatory effects either directly, via the anti-inflammatory subset of beta adrenergic receptors on macrophages [135], or indirectly, by stimulating a subset of CD4+ T-cells thought to be capable of releasing acetylcholine [132, 136], which could in turn activate the anti-inflammatory nAChRs within the spleen.

Importantly, the cholinergic anti-inflammatory pathway may not be confined to the spleen, and the anti-inflammatory actions of the vagus may also be exerted via other peripheral lymphoid tissues such as the gut [136-138] or the bone marrow. The effect of vagus on the bone marrow could be particularly pertinent in hypertension and other forms of CVD, which are characterized by inflammation and a dampened vagal reflex. This view is supported by our preliminary data indicating that direct administration of NE into the bone marrow increases mobilization of pro-inflammatory T-cells, which can be attenuated by ACh, suggesting that the bone marrow itself may be a beneficiary of the anti-inflammatory cholinergic pathway. The bone marrow, like the spleen, does not have a direct vagal input; however, the vagal message may be relayed through the superior cervical ganglion, as it contains both the vagal input [139] and the sympathetic output innervating the bone marrow [101]. Therefore, the vagal anti-inflammatory input to the bone marrow could be similar to that described in the spleen [136, 140].

Francois Abboud's group recently demonstrated that the cholinergic input to the spleen was pro-inflammatory in the pre-hypertensive SHR, whereas there was a pronounced anti-inflammatory cholinergic modulation of the innate IS in the WKY [67], suggesting that a dysfunctional ANS-IS communication may precede the development of hypertension. It is attractive to propose that the anti-inflammatory cholinergic input to the bone marrow could also be processed in a similar dysfunctional fashion, causing pro-inflammatory effects in the SHR and anti-inflammatory effects in the WKY. Alternatively, reduced cholinergic release in the periphery due to dampened vagal activity in hypertension may have a direct anti-inflammatory effect on the bone marrow, as suggested by our preliminary data showing that the activation of the bone marrow ICs can be inhibited by direct application of ACh.

In summary, recent findings have underscored the importance of sympathetic and parasympathetic modulation of IS responses. We propose that an imbalance between sympathetic and parasympathetic control could be associated with several pathologies, including hypertension, CVD and diabetes. Furthermore, the anti-inflammatory parasympathetic axis may present as a potential therapeutic target in hypertension. The role of the vagus and of the bone marrow in modulating IS responses is an area of emerging interest.

5. Possible role of sensory input

A plethora of evidence describes how the ANS controls immune responses, as discussed in the previous section. There is also good evidence of a bidirectional communication between the CNS and the IS. As mentioned before, the vagal sensory afferents are able to detect cytokine levels in the periphery and relay the message to the brainstem nuclei, subsequently activating the vagal efferents in an immune reflex loop.

Whether the bone marrow is able to relay messages back to the brain in a similar fashion may be of great interest in relation to CVD. Many of the fibers innervating the bone marrow, in addition to the sympathetic, are primary afferent sensory fibers [141-143]. Pain studies

have demonstrated that the periosteum, mineralized bone, and the bone marrow are innervated by various sensory nerve fibers, including thickly and thinly myelinated A-fibers, as well as the peptide-rich C-fibers [144, 145]. These fibers are able to detect multiple environmental factors, including the inflammatory cytokines, which enhance the excitability of the sensory nerve fibers [146]. In hypertensive patients who have increased levels of systemic inflammation, it is possible that the bone marrow can directly relay the pro-inflammatory message back to the CNS. In line with this, the nociceptive afferent sensory message from the periphery is processed in brainstem pre-sympathetic nuclei such as the NTS [147], in close proximity to the vagus. Nociception has been shown to attenuate the parasympathetic, but not the sympathetic, arm of the baroreflex within the NTS [148, 149] by dampening the vagal activity. Moreover, direct electrical stimulation of the bone marrow increases blood pressure [150], supporting a direct afferent neuronal input to the pre-sympathetic areas of the brain. Both sensory and sympathetic nerve fibers in the limbs are able to sprout in response to inflammation [151, 152], suggesting high responsiveness of the sensory fibers to pro-inflammatory signals and providing additional support for the concept of bidirectional communication in the system. The increased inflammatory responses seen in hypertension may be directly related to the increased sympathetic activity and originating in the bone marrow.

In light of the evidence presented here, we propose that the dysfunctional cholinergic anti-inflammatory reflex stimulates inflammation in the bone marrow, and thus contributes to the pathophysiology of neurogenic hypertension. Understanding the sensory input from the bone marrow may hold the answers to the mechanisms underlying the establishment and maintenance of hypertension.

The recent discovery of a new RAS member by Robson Santos's group poses many interesting questions about the role of the RAS in sensory afferent nerve function. Alamandine is a heptapeptide formed from angiotensin A or angiotensin-(1-7) and is present *in vivo* [153]. It acts through the MrgD receptor, a member of the Mas-related gene receptor family that is found in many sensory structures, particularly in skin [154, 155]. Although the fibers expressing this novel RAS-related receptor are not present in the bone marrow [144], these sensory fibers could be important in other peripheral organs and even the vasculature. Recently, MrgD receptors have been found to regulate mast cell activation during intestinal inflammation [156, 157]. Therefore, it is possible that there is a direct link between the peripheral RAS communicating to the brain through afferent nerves and the inflammatory response in hypertension. Interestingly, sensory dorsal root ganglion neurons also express functional Ang II receptors [158, 159], suggesting a role for multiple members of the RAS in this novel bidirectional communication loop.

6. Role of bone marrow in hypertension and CVD

As inferred in the previous section, the importance of bone marrow in neurogenic hypertension is extremely undervalued. Studies suggest that the bone marrow harbors memory T-cells, and most importantly, it is a site for the initiation of T-cell activation responses [160]. Given the importance of T-cell activation in hypertension, discussed in earlier sections, the bone marrow may be a key organ in neurogenic hypertension. The bone marrow is also the primary source of EPCs [161], which play a particularly important role in endothelial repair in the setting of arterial and renal injury following inflammatory and other pro-hypertensive stimuli [162-164]. Compromising the ability of the EPCs to repair endothelial damage may perpetuate the pathophysiology of hypertension.

In the bone marrow, EPCs are localized in the stem cell niche. This niche is particularly important for controlling the ability of these cells to mobilize and differentiate [165], and

has recently been shown to have immune privilege provided by Treg cells [166]. It is important, however, to note that stem cells and lymphoid progenitors occupy separate bone marrow compartments [167]. EPCs respond differently to various stimuli. For example, acute inflammatory stimuli trigger EPC mobilization, while chronic inflammation can have the opposite effect and actually decrease the number of circulating EPCs [168]. In addition to inflammation, EPCs are also able to respond to autonomic stimulation. Recently, it has been suggested that beta-2 adrenergic receptor stimulation can improve EPC function [169]. However, chronic elevation in bone marrow NE may impair the function of EPCs, and this may be important in the context of hypertension. These observations are strengthening the link between the nervous system and the bone marrow.

There is evidence linking bone pathologies with vascular lesions in chronic kidney disease, including end-stage kidney disease [170-172]. Further, bone vascularization is of particular interest in the context of hypertension and other forms of CVD, since the cross-talk between the ANS and the bone marrow vasculature could be a key mechanism of hypertension pathophysiology. As in other vascular beds, NE acts as a vasoconstrictor in the bone marrow and plays an important role in controlling blood flow [173]. Within the bone marrow, there is an oxygen gradient responsible for maintaining healthy cell environments. Hematopoietic stem cells are found in the osteoblastic niche, which is hypoxic, and upon maturation, travel to the vascular niche where they are able to differentiate [174]. It is possible that in the context of neurogenic hypertension, which presents with increased circulating NE, there may be extensive vasoconstriction in the bone marrow, creating a hypoxic environment that could negatively modulate stem and progenitor cell function, as well as enhance local inflammatory responses. These ideas merit further investigation in the context of hypertension, as improvement of the bone marrow blood flow may present a novel therapeutic target for that condition.

7. Conclusion

In the present review we have discussed the interplay between the ANS and the IS. Both systems hold particular importance in the pathophysiology of hypertension. We propose that the relevance of bone marrow in the field of CVD is greatly undervalued. The bone marrow is a crucial meeting point for neural, immune, and vascular networks. Afferent sensory fibers may relay important inflammatory signals to the brain, and sympathetic efferent fibers could affect both inflammatory and progenitor cells in the bone marrow niches. The interplay among these systems in the bone marrow is likely complex. It is important to determine the nature and origins of the signals transmitted to the brain by the bone marrow afferents, as well as to determine how the vasculature within the bone marrow is regulated in hypertensive subjects. .

There is current interest in studying these systems in subjects with pre-hypertension. The finding of increased inflammation and autonomic dysfunction in pre-hypertensive patients and animals has led to emerging interest in examining the time course of the development of hypertension and identifying novel biomarkers that may yield new therapeutic targets for prevention of high blood pressure. While increasing amounts of data suggest that both increasing sympathetic activity and inflammatory responses precede increases in blood pressure, the exact timing of these events and their specific roles in the development of hypertension remain to be elucidated. Therefore, the question remains: which comes first, inflammation or hypertension?

We propose the following unifying hypothesis to summarize our discussion (Fig. 1). Hypertensive stimuli, including Ang II, work centrally to activate both microglia and neurons. Changes in neuronal activity lead to dysfunction of ANS signaling to the periphery,

including decreased parasympathetic efferent signaling through the vagus and increase sympathetic efferent signaling through the sympathetic chain to key lymphoid organs, such as the spleen and bone marrow. Autonomic dysfunction in these organs works to increase inflammatory responses, such as the production of pro-inflammatory cytokines and cells, as well as to inhibit EPC function and ultimately vascular repair. Elevation in the pro-inflammatory factors may be detected by the sensory afferents in the periphery, including those within the bone marrow, which may relay the message to the brainstem cardioregulatory areas, ultimately contributing to dampening of the vagal anti-inflammatory reflex and perpetuating the pro-inflammatory responses via the feed-forward loop. These increases in peripheral inflammation and endothelial dysfunction ultimately lead to the vascular, renal, and cardiac lesions of hypertension (Fig. 1).

Despite important recent advances in the field, several key questions remain. First, what are the underlying mechanisms triggering both peripheral and central inflammation? Can the vagus relay messages to the bone marrow? Can bone marrow afferent signals modify function in cardioregulatory regions of the brain? Better understanding of the balance between the pro-inflammatory sympathetic system and the anti-inflammatory parasympathetic system will provide many answers to these questions.

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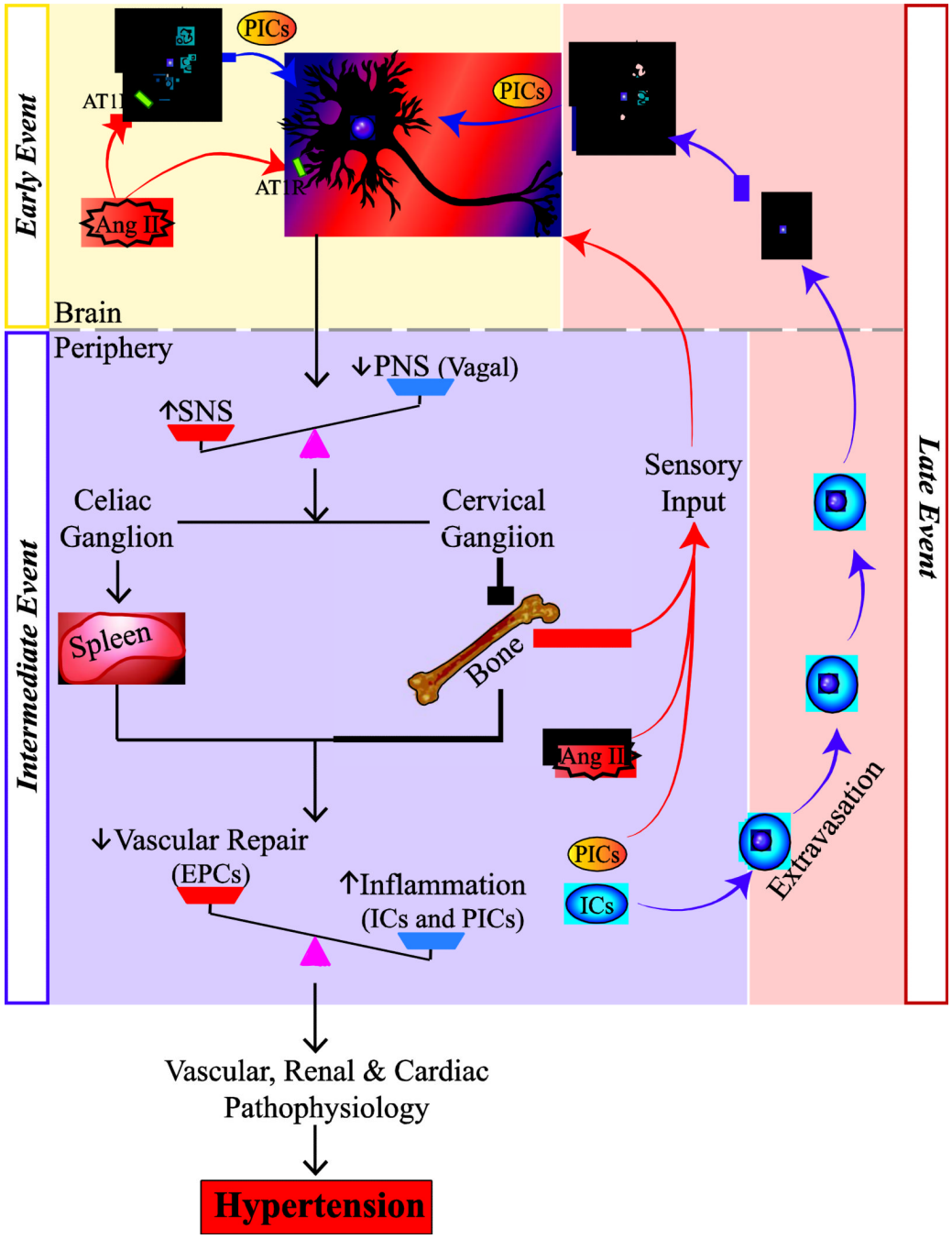

Fig. 1. Proposed hypothesis of a dysfunctional brain-bone marrow communication in the development and establishment of hypertension

Activation of microglia in cardioregulatory areas of the brain is an *early event* in the development of hypertension. AngII and other pro-hypertensive stimuli activate both microglia and neurons, thus altering neuronal activity in the hypothalamus and the brainstem. These central responses give rise to *intermediate events* in the periphery, which include increased sympathetic and decreased parasympathetic signaling to the spleen and bone marrow, leading to increased inflammation and impairment in vascular repair. Moreover, the bone marrow sensory afferents may relay information about the inflammation to the brain. Finally, the *late event* involves the extravasation of bone marrow-derived

inflammatory progenitors in brain that differentiate into microglia, further enhancing neuroinflammation in the autonomic regulatory areas of brain, thus facilitating the development of hypertension.

Abbreviations- PICs: pro-inflammatory cytokines; ICs: inflammatory cells; EPCs: endothelial progenitor cells; SNS: sympathetic nervous system; PNS: parasympathetic nervous system