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Review

Novel adaptive and innate immunity targets in hypertension

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ABSTRACT

Hypertension is a worldwide epidemic and global health concern as it is a major risk factor for the development of cardiovascular diseases. A relationship between the immune system and its contributing role to the pathogenesis of hypertension has been long established, but substantial advancements within the last few years have dissected specific causal molecular mechanisms. This review will briefly examine these recent studies exploring the involvement of either innate or adaptive immunity pathways. Such pathways to be discussed include innate immunity factors such as antigen presenting cells and pattern recognition receptors, adaptive immune elements including T and B lymphocytes, and more specifically, the emerging role of T regulatory cells, as well as the potential of cytokines and chemokines to serve as signaling messengers connecting innate and adaptive immunity. Together, we summarize these studies to provide new perspective for what will hopefully lead to more targeted approaches to manipulate the immune system as hypertensive therapy.

Contents

Over 50 years of evidence has established a prominent role for adaptive and innate immune mechanisms in the development of hypertension (HTN), vascular disease and renal disease [1–6]. Our lab's interest in immune mechanisms in HTN arose from studies in which we observed that inflammation amplifies salt-sensitive hypertension (SSHTN) and end-organ damage in Dahl SS rats [4]. In Dahl SS rats, as in the clinical condition, HTN is greatly accelerated by a high salt diet [4]. Moreover, inflammation is a common feature of experimental and clinical HTN, with lymphocytes and macrophages localizing to regions of injury [4,7–9]. The amplifying effect of immune mechanisms on HTN are illustrated in Fig. 1, in which we demonstrate the change in mean arterial blood pressure in Dahl SS rats and Dahl SS deficient in T and B lymphocytes (SS-Rag1$^{-/-}$) [10]. The difference in the degree of salt-sensitive hypertension between the groups illustrates the role of immune mechanisms to amplify the HTN disease phenotype. As summarized below, a number of studies have illustrated the importance of adaptive and innate immune mechanisms in HTN; these mechanisms are the focus of this brief review.

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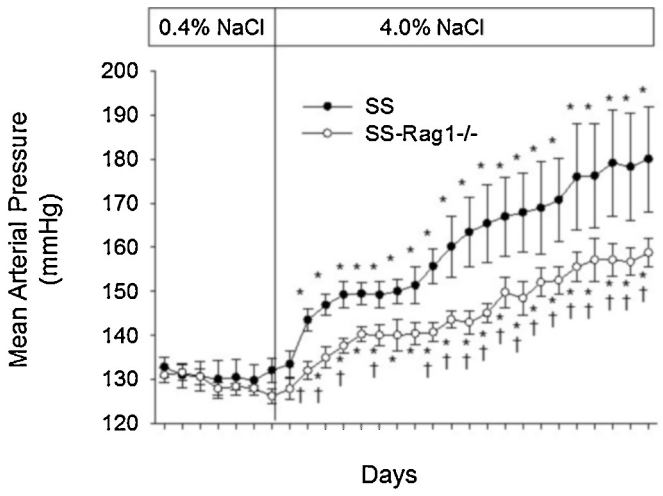

Fig. 1. Development of salt-sensitive hypertension in Dahl SS rats (SS) and SS rats deficient in T- and B-lymphocytes due to the genetic deletion mutation in *Rag1* (SS-Rag1$^{-/-}$). *$P < 0.05$ *vs* final day of low salt in the same group; †$P < 0.05$ *vs* SS on the same day; $n = 4$–5/group.

Source: Reproduced with permission from [10].

1. Targets of adaptive immunity

1.1. T and B lymphocytes

The hallmark cell types of the adaptive immune system are T and B lymphocytes. T cells are activated after interaction with an antigen presenting cell (APC), then proliferate and differentiate into one of three effector subtypes: cytotoxic, helper, or regulatory T cells. Recent work shows an evolving role of the T cell in the development of HTN and chronic kidney disease. Studies utilizing genetic knockout of the recombination activating gene1 (RAG1) gene, which is essential for T and B cell maturation, in the mouse [11] and later the rat [10] have shown a clear attenuation in the development of angiotensin II (AngII)-induced and SSHTN (Fig. 1). Genetic knockout of the CD247 gene, essential in T cell survival and receptor function, led to a severe depletion of T cells but left B cells intact. Compared to wild type rats, Dahl SS with CD247 knockout demonstrated an attenuation of SSHTN and end-organ damage [12]. Rodriguez-Iturbe et al. also showed that systemic administration of the immunosuppressive agent mycophenolate mofetil led to a decrease in infiltrating immune cells in the kidney and a reduction in blood pressure in spontaneously hypertensive rats (SHRs) [13]. Clearly, affecting lymphocyte populations on a global scale has been shown to have dramatic effects in hypertensive animal models.

More recently, scientists have focused upon mechanisms of T cell survival and activation in HTN. One gene product required for T cell survival is the receptor tyrosine kinase TAM family member Axl. Korshunov et al. first demonstrated attenuation of DOCA/salt-induced HTN in an Axl$^{-/-}$ mouse strain and also observed improved endothelium-dependent vasorelaxation compared to Axl$^{+/+}$ [14]. It was later discovered that Axl$^{-/-}$ mice exhibited severe depletion of peripheral blood T and B lymphocytes [15], and adoptive transfer of Axl$^{-/-}$Rag$^{+/+}$ T cells into Axl$^{+/+}$Rag$^{-/-}$ mice had significantly slower CD4+ repopulation than transfer of Axl$^{+/+}$Rag$^{+/+}$ T cells, underscoring the importance of Axl in T cell expansion.

Though adaptive immunity is important in the development of hypertension, the mechanisms activating these immune mechanisms are largely unknown. Seminal work published by the Harrison group revealed that the activation of T cells in AngII-induced HTN was dependent upon the production of highly reactive isoketals by dendritic cells [16]; moreover, the administration of various isoketal scavenging agents demonstrated a blunted hypertensive response. In addition, the isoketal scavenger 2-HOBA reduced AngII-induced renal fibrosis, renal T cell infiltration, IL-6 and IL-1β cytokine production, and T cell survival and proliferation. In an additional study, treatment with 2-HOBA or the antioxidant Tempol led to a decrease in production of IL-17A and IFNγ by T cells in tgsm/p22phox mice. Though it is well-established that reactive oxygen species (ROS) are linked to vascular damage in HTN [17], these studies provide a link to adaptive immunity.

Similarly, work by Rodriguez-Iturbe and colleagues indicated that heat shock proteins (HSP), may also serve as an antigen triggering adaptive immunity in HTN [18,19]. Their work indicated that HSP70 could serve as an antigen mediating cellular immunity in experimental and human HTN. Studies by Macconi et al. demonstrated that proteolytic cleavage of albumin in proximal tubule cells could generate antigenic peptides [20]. The isoketal protein adducts, heat shock proteins, albumin cleavage products, or other molecules may serve as antigens which trigger the adaptive immune responses which amplify HTN and end organ damage.

Though the complete depletion of the T cell population has generated many interesting insights, the role of specific T cell subtypes has not been as deeply interrogated. In a study investigating the role of AngII on human T cells in a humanized mouse model, AngII treatment was found to increase total CD3+ and CD4+ T helper cells as well as CD45RO+ T memory cells in the kidney, which was abolished by the prevention of HTN through coadministration of hydrochlorthiazide (HZT) and hydralazine [21]. By controlling blood pressure, these experiments demonstrated that AngII did not directly affect the activation state of T cells. Trott et al. also investigated the role of specific T cell subtypes in AngII as well as DOCA/salt-induced HTN and observed a blunted response in CD8$^{-/-}$ mice but not in MHCII$^{-/-}$ or CD4$^{-/-}$ mice [22]. In adoptive T cell transfer experiments into Rag1$^{-/-}$ mice, transfer of CD8+ cytotoxic T cells significantly increased blood pressure, whereas transfer of CD4+/CD25− T cells did not. Although these results implicate a more direct effect of CD8+ cytotoxic T cells on the hypertensive phenotype, the role of CD4+ helper T cells needs to be explored more thoroughly.

Compared to T cells, the contribution of B cells to hypertensive pathology is being investigated at a much slower pace despite clear evidence that antibodies are elevated in patients with essential HTN [23]. Chan et al. explicitly investigated the role of B cells in AngII-induced HTN, and found AngII increased B cell activation, the number of plasmablasts and plasma cells, and serum IgG [24]. B cell activating factor receptor deficient (BAFF-R$^{-/-}$) mice that lack B cells did not exhibit the same increase in blood pressure observed in WT mice in response to AngII, but importantly, adoptive transfer of B cells into BAFF-R$^{-/-}$ mice restored AngII-induced HTN. In apparent contradiction to the study by Trott et al., who found an increase in CD4+ and CD8+ T cells in the kidney, analysis of T cell subsets revealed no change in CD8+ cells and an increase in CD4+ cells in the aorta upon AngII administration. The integral role of B cells in adaptive immunity as well as understanding its crosstalk with T cells will be important in the holistic investigation of HTN pathogenesis.

1.2. T regulatory cells

T regulatory cells (Tregs) are a specialized subset of T cells that are responsible for the maintenance of immune homeostasis and self-tolerance [25]. In humans, Tregs comprise about 5–10% of peripheral CD4+ T cells, and they express CD4+, CD25+ and forkhead/winged helix transcription factor P3 (FoxP3) [26]. FoxP3 is a major regulatory gene required for the development and regulatory function of Tregs [27]. Tregs are reported to play a pivotal role of suppression of both the innate and the adaptive immune system.