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Th17/Treg Imbalance in Hypertension

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Abstract

The T helper 17 cells (Th17 cells) are a type of T cells that plays an important role in the adaptive immune system. Studies show that Th17/regulatory T cells (Treg) imbalance, as characterized by increased Th17 and decreased Treg, plays a critical role in inflammation in various cardiovascular diseases including hypertension. The study of Th17/Treg imbalance in hypertension may uncover important triggers and endogenous modulators of the disease, and lead to new treatment strategies. This review outlines current insights into Th17/Treg frontiers associated with hypertension and discusses the questions that remain in this field.

Keywords: T helper 17 cells; Regulatory T cells; Hypertension; Target organ damage

Introduction

Recent data demonstrated that CD4+ T lymphocytes-mediated immunity contributes to various cardiovascular diseases including hypertension. $CD4^+$ T lymphocytes, also called T helper cells (Th cells), consist of Th1, Th2, Th17 and Treg cells. Among them, Th1 cells mainly mediate host defense against intracellular pathogens by expressing interleukin (IL)-2, interferon γ (IFN-γ), and tumour necrosis factor β (TNF-β) [1]. Th2 cells primarily express IL-4, IL-5, IL-6, and IL-13 in response to extracellular stimuli. An imbalance in Th1/Th2 subsets is implicated in resistance and susceptibility to infection, the pathogenesis of autoimmune diseases such as diabetes [2]{Zhang, 2014 #995}, and the development of atherosclerosis [3,4]. Th17 cells represent a novel subset of Th cells that produces the proinflammatory IL17 [5]. There are six isoforms of IL-17, classified as A-F, among them IL17A is the most important and the most widely studied [6,7]. Th17 cells protect against extracellular bacteria and fungi. Treg cells suppress ongoing immune responses through the secretion transforming growth factor β1 (TGF-β1) and IL-10. Furthermore, Treg cells are central in mediating peripheral tolerance and are involved in the maintenance of tolerance to self-antigens [8].

Importantly, the differentiation of Th17 and Treg is mutually inhibitory [9]. For example, the differentiation of Th17 cells requires a unique lineage-specific transcription factor, retinoid-related orphan receptor γt (RORγt), while Treg cells employ forkhead box P3 (Foxp3) as a key transcription factor. TGF-β1 is a critical factor in common for Th17 and Treg cells, since it induces the expression of Foxp3 and RORγt in T cell receptor (TCR)-stimulated naive CD4+ cells [10-12]. In the presence of pro-inflammatory cytokines IL-6 or IL-21, the TGF-β1 induced-Foxp3 expression is reduced and RORγt expression is up-regulated, leading to increased Th17/Treg ratio. In absence of IL-6 or IL-21, however, TGF-β1 is unable to initiate Th17 differentiation *in vitro*. TGF-β1 then promotes Treg differentiation that maintains immune tolerance. In addition, Foxp3 also mediates RORγt inhibition, resulting in decreased IL-17 and IL-23 expression [10-12]. There are increasing evidence indicates that Th17, Treg and Th17/Treg balance are involved in hypertension and target organ damage [13,14]. In this review, we will discuss how Th17, Treg and Th17/Treg balance contribute to blood pressure elevation and target organ damage.

Th17 Cells and Hypertension

There are emerging evidences that Th17 cells and IL17 are involved in the maintenance of angiotensin II-induced hypertension, and deoxycorticosterone acetate (DOCA)-salt-induced hypertension. For example, it has been reported that hypertension was not sustained in IL17-/- mice, reaching levels 30 mm Hg lower than in wild type mice by 4 weeks of angiotensin II infusion, even the initial hypertensive response to angiotensin II infusion was similar [15]. Vessels from IL17-/- mice showed decreased superoxide production, and reduced aortic T cell infiltration in response to angiotensin II stimulation [15]. It has been shown that IL-7 inhibited the activity of endothelial nitric oxide synthase (eNOS) by promoting threonine 495 phosphorylation in a Rho kinase-dependent manner in endothelial cells, thereby leading to endothelial dysfunction and increased blood pressure [16]. Wu et al. reported collagen deposition and aortic stiffening did not occur in IL-17A-/- mice, and *in vitro* study indicated that IL-17 induced mRNA expression of collagens I, III and V via activation of p38 MAP kinase [17]. These results suggest that IL-17A acts as a causative cytokine in aortic stiffening [17]. In addition, it has been reported that mineralocorticoid receptor activation contributed to fibrosis partially through Th17/Treg/IL-17-dependent inflammatory mechanism [18]. Furthermore, Krebs et al. showed that genetic disruption of the IL-23/IL-17 axis attenuated glomerular injury and renal infiltration of γδ T cells in DOCA + angiotensin II-induced albuminuria and hypertensive renal damage [19]. However, Marko et al. reported that IL-23 antibody and IL-17A antibody treatment did not reduce cardiac hypertrophy, fibrosis, and electric remodeling despite mildly reduced inflammation in angitoensin II-induced hypertensive mice [20]. These results suggest that Th17 signaling pathway may not play a role in angiotensin II-induced cardiac damage [20]. Therefore, further studies are needed to

evaluate the involvement of Th17 signaling pathway in angiotensin II-induced hypertension.

Treg Cells and Hypertension

It has been demonstrated that decreased Treg cells were involved in angiotensin II-induced hypertension, in DOCA-salt-induced hypertension and in spontaneously hypertensive hypertension (SHR). For example, Barhoumi et al. reported that angiotensin II caused a significant decrease of Foxp3+ cells in the renal cortex. Furthermore, they found that Treg cells injection inhibited angiotensin II-induced hypertensive changes including increased systolic blood pressure, vascular/cardiac NADPH oxidase activation, impaired vasodilatory responses, increased vascular stiffness, increased expression of mesenteric artery vascular cell adhesion molecules, and increased aortic macrophage infiltration and T-cell infiltration [21]. In addition, Kvakan et al. demonstrated that Treg transfer interfered ameliorated cardiac hypertrophy and fibrosis, TNF-α expression, immune cell infiltration in angiotensin II-induced hypertensive mice [22]. It has been demonstrated that Treg transfer prevented hypertensive changes in DOCA-salt-induced hypertension including increased blood pressure, decreased vasodilation, vascular remodeling of resistance arteries [23]. These changes may be related to the decreased NADPH oxidase activity and superoxide production in aorta, kidney and heart after Treg treatment [23]. Finally, Katsuk et al. reported that splenic Treg infiltration was decreased with age in SHR before the onset of hypertension. Importantly splenic sympathetic denervation in pre hypertensive SHR attenuated the reduction in splenic Treg cells and delayed the development of hypertension, suggesting that splenic sympathetic nerve activation is involved in both the decrease in Treg cells and the progression of hypertension in SHR [24].

It has been shown that IL-10 has protective functions in hypertension [25]. For example, Didion reported that the infusion of angiotensin II doubled superoxide production in carotid arteries of IL-10-/- mice, but not in WT mice, and that angiotensin II-infused IL-10-/- mice showed markedly impaired vasodilatation, while having no effect in vessels of wild type mice [26]. These results indicated that IL10-deficiency is involved in increased superoxide production and oxidative stress in artery after the infusion of angiotensin II, leading to vascular dysfunction. It has been shown that adoptive transfer of Treg cells has been shown to lower angiotensin II- and aldosterone-induced cardiac fibrosis, electrical remodeling, the effect on blood pressure of Treg cells is not the same. Kvakan et al. demonstrated that Treg cell transfer did not affect the development of hypertension, indicating that the cardiac protection was blood pressure independent. However, Barhoumi et al. showed that adoptive transfer of Treg cells prevented Ang II-induced progressive increase of systolic blood pressure both in tail-cuff measurement and in telemetry measurement. Taken together, these studies suggest that Treg cells exert an anti-hypertensive role and protect target organ damage in various hypertensive animal models.

Th17/Treg Imbalance and Hypertension

The balance between Th17 and Treg cells also play a role in the development/prevention of hypertension since the differentiation of Th17 and Treg are mutually inhibitory [27]. Xie showed that Th17/Treg imbalance was involved in the formation and progression of atherosclerosis [28]. Amador et al. demonstrated that there was an activation of Th17 cells and down regulation of foxp3 mRNA in peripheral tissues, heart, and kidneys in DOCA salt-treated rats [18]. Furthermore, treatment with spironolactone, a specific pharmacologic antagonist of aldosterone, prevented Th17 cell activation and increased numbers of Treg cells in DOCA salt rats, suggesting that mineralocorticoid receptor activation alters the Th17/Treg pathway in DOCA salt hypertension. Another study showed that excess dietary sodium intake increased induction of proinflammatory Th17 cells and impact autoimmunity by inhibiting the function of Treg cells [29]. Importantly, there are accumulating clinical data showing that anti-hypertension treatment attenuated vascular changes in a Th17/Treg-dependent manner. For example, an randomized, prospective, double-blind, placebo-controlled trial study shows that there was a significant synergistic effect of combination of telmisartan with rosuvastatin on ameliorating carotid intima-media thickness (IMT) and Th17/Treg functional imbalance, suggesting a role of Th17/Treg imbalance in carotid IMT [30].

In summary, there are accumulating evidence showing that Th17, Treg, and Th17/Treg imbalance are involved in the initiation and development of increased blood pressure, target organ damage in angiotensin II-induced hypertension, salt-sensitive hypertension, and genetic hypertension. Studies on Th17/Treg may provide a new direction for the prevention and treatment of target organ damage associated with hypertension.

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