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COMMENT

# Association between the gut microbiome and the renin-angiotensin-aldosterone system: a possible link via the activation of the immune system

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**Keywords** Gut microbiota · Renin-angiotensin-aldosterone system (RAAS) · Th17/Treg ratio · Short-chain fatty acid (SFCA)

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Hypertension, the major risk factor for cardiovascular disease, is a major health issue that affects people worldwide. Generally, hypertension is the result of the superposition of many factors, comprising both genetic and environmental factors. The classic pathogenesis of hypertension involves hyperactivity of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system (RAAS), and vascular endothelial dysfunction. Recent evidence shows that gut microbiota play a role in the development of cardiovascular disease, including hypertension [1]. Germ-free mice are resistant to hypertension and vascular dysfunction after angiotensin II (Ang II) infusion. On the other hand, transplantation of the gut microbiome from hypertensive subjects increases blood pressure (BP) in germ-free recipient mice, suggesting a causal role of the gut microbiome in the development of hypertension. The normal composition of the gut microbiome is essential to maintain the health of the body, and an imbalance in the gut microbiome is closely related to the occurrence and progression of hypertension. Robles-Vera et al. found that the number of inflammatory cells in the serum and intestinal tissue of hypertensive patients increased significantly, while the number of the genus of *Bifidobacterium* decreased [2].

Recently, Mizoguchi et al. [3] published Shika-machi Super Preventive Health Examination results of 377 participants from the general population aged 40 years or older in *Hypertension Research*. The results showed that the genus of *Blautia, Bacteroides, Akkermansia*, and *Bifidobacterium* were associated with RAAS parameters. The authors showed that *Blautia* was associated with plasma aldosterone concentrations (PACs) and proposed the possibility of new therapeutic approaches using probiotics and prebiotics for many RAAS-related diseases [3].

A considerable number of studies have shown that elevated renin and aldosterone levels are predictors of adverse outcomes in many diseases, such as myocardial infarction, renal insufficiency, and heart failure. Furthermore, it was demonstrated that aldosterone modulates adaptive immune responses [4]. Aldosterone can bind to the mineralocorticoid receptor (MR) in antigen-presenting cells (APCs), such as dendritic cells and macrophages, and activated APCs promote the polarization of Th17 effector lymphocytes (Th17 cells), which produce a wide variety of proinflammatory cytokines, including IL-17A. Ang II-induced hypertension is associated with increased production of IL-17A by Th17 cells. Interestingly, IL-17A induces cardiac fibrosis and ventricular dysfunction without elevation of BP in spontaneously hypertensive rats (SHRs) [5]. Thus, activation of MR resulting in an increase in Th17 cells could contribute to cardiac fibrosis through a BP-independent mechanism. Moreover, there is a report that a strong positive correlation between the Th17 to regulatory T lymphocyte (Treg) cell ratio and aldosterone to renin ratio (ARR) was found in patients with primary aldosteronism (PA) [6]. ARR has been utilized as a basic parameter for screening for PA based on clinical practice guidelines. It has been shown that aldosterone-induced augmentation of BP, endothelial dysfunction, vascular remodeling, and oxidative stress could all be prevented by adoptive transfer of Treg cells [7]. In addition, a higher Th17/Treg cell ratio was seen in the kidney and heart of hypertensive rats; however, this ratio could be restored in animals that received spironolactone treatment [5]. On the other hand, in the vasculature, Th17 cells promoted vascular fibrosis, while Treg

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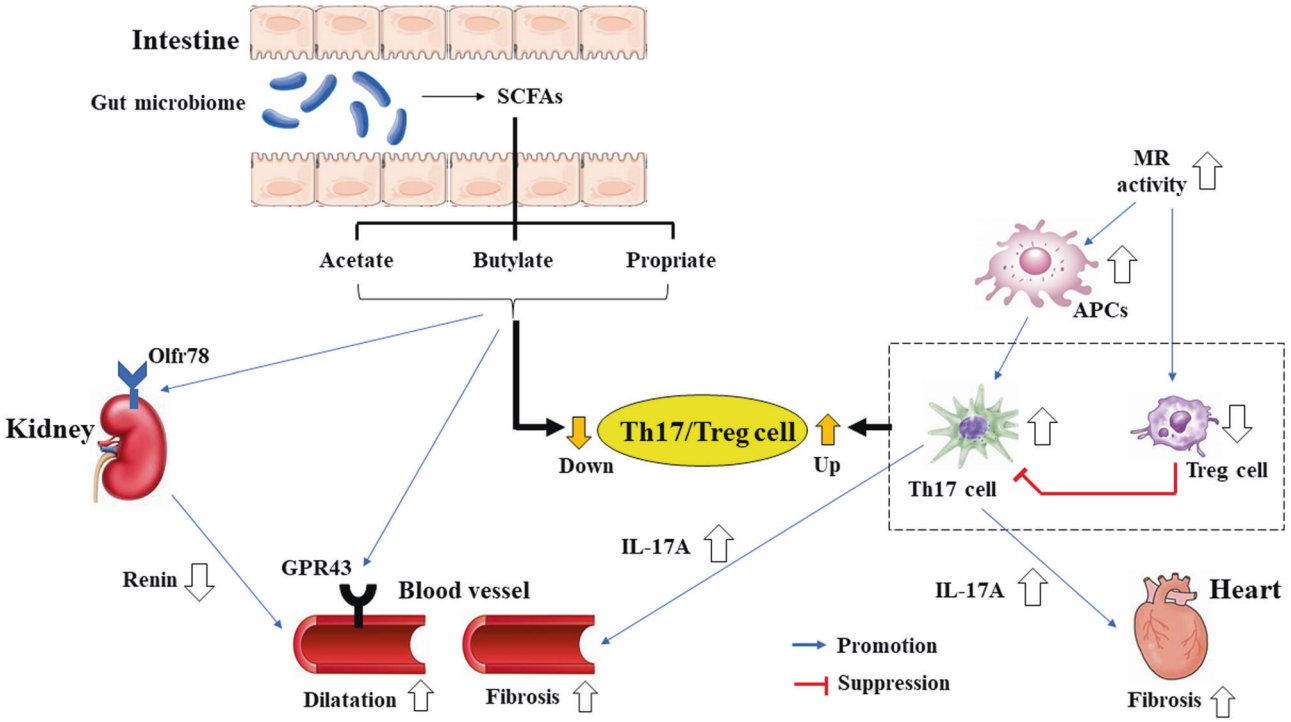


**Fig. 1** Relevant mechanisms through which gut microbiota regulate blood pressure. Gut microbiota can regulate blood pressure through multiple pathways. SCFA short-chain fatty acid, MR mineralocorticoid receptor, APCs antigen-presenting cells, Th17 Th17 effector lymphocytes, Treg regulatory T lymphocytes

cells prevented many of the vascular remodeling effects in Ang II-induced hypertension models [7]. Specifically, adoptive transfer of Treg cells attenuated Ang II-induced cardiac hypertrophy and fibrosis, vascular medial thickening, and vascular oxidative stress. Furthermore, Treg cells in which MR is also expressed suppressed Th17 cell polarization, and the expression of IL-17 and MR activation suppressed Treg cell function. Thus, it is suggested that an imbalance in the Th17/Treg cell ratio could be implicated in the hypertension and organ damage caused by MR activation. Overall, by changing the balance of T lymphocyte subsets with an increase in Th17 cells and a decrease in Treg cells, RAAS activation in the immune system might contribute to cardiac and vascular fibrosis.

Gut microbial metabolites play an important role in maintaining cardiovascular health and intestinal homeostasis [8]. Researchers have been exploring the mechanism of BP reduction after the consumption of probiotic preparations. Probiotics can use their metabolites to regulate BP. Short-chain fatty acids (SCFAs), which are gut microbial metabolites, can regulate BP via the activation of G protein-coupled receptors (GPCRs). For example, SCFAs can interact with at least four GPCRs to regulate BP, including G protein-coupled receptor 41 (GPR41), G protein-coupled receptor 43 (GPR43), G protein-coupled receptor 109A (GPR109A) and olfactory receptor 78 (Olfr78) [9]. SCFAs regulate BP through GPR41 and Olfr78. Exogenous supplementation with propionate, an SCFA, effectively reduced BP in Ang II-induced hypertensive rats, and this effect was related to the release of intracellular $Ca^{2+}$ through the activation of GPR41 in the vascular endothelium [10]. Olfr78 is expressed in the renal juxtaglomerular apparatus, where it modulates renin secretion. Propionate also regulates the secretion levels of renin in blood and modulates BP through Olfr78. Together, SCFAs, a key class of gut microbial metabolites, can regulate BP by activating special GPCRs.

Modulation of the immune-inflammatory response is another route through which SCFAs regulate BP. Supplementation with SCFAs can also regulate BP through modulation of Th17 and Treg cells. In Ang II-induced hypertensive rats, exogenous propionate exerts antihypertensive, anti-inflammatory, and anti-arteriosclerotic effects, which may be related to the immune-inflammatory response mediated by Th17 and/or Treg cells (Fig. 1) [11]. Furthermore, the administration of the species of *Bifidobacterium breve* to SHRs reduced BP by promoting butyrate-producing bacteria, and the hypotensive effects of butyrate and acetate might be achieved by restoring the balance of Th17/Treg cells in mesenteric lymph nodes [12]. Treatment with the species of *Bifidobacterium breve* CECT7263 prevented hypertension through the repair of renal damage, the restoration of balance in the Th17/Treg cell ratio, and the repair of endothelial dysfunction in SHRs,

indicating that the genus of *Bifidobacterium* is a probiotic and participates in the regulation of body immunity [2].

The present paper [3] raised several concerns. First, in this study, the authors have shown that the abundance ratio of *Bifidobacterium* was significantly high in the high PAC group. However, as described above, *Bifidobacterium* is considered to have beneficial effects on BP. Thus, it is necessary to elucidate the detailed mechanism by which the abundance ratio of the genus of *Bifidobacterium* is increased in high PACs. Second, the authors listed the genus of *Blautia*, *Akkermansia*, the order of *Ruminococcaceae UCG-002*, the genus of *Dialister* and *Ruminococcus 2* in addition to the genus of *Bifidobacterium* as the gut microbiota associated with RAAS. In the high plasma renin activity group, the abundance ratio of *Blautia* was significantly high, whereas those of *Akkermansia* and *Ruminococcaceae UCG-002* were low. Moreover, in the high PAC group, the abundance ratios of *Dialister* and *Bifidobacterium* were significantly high, whereas that of *Ruminococcus 2* was low. Additionally, in the high ARR group, the abundance of *Akkermansia* was significantly high. These gut bacteria produce SCFAs such as propionate and acetate [3]. However, much less is known about the relationship between the gut microbiota and the RAAS, and the mechanisms by which the RAAS modulates gut microbiota have not been fully clarified. Additional preclinical and clinical studies are needed to answer this question.

The recent paper [3] obviously opened the door of the association between the gut microbiome and the RAAS using human specimens from the Japanese general population. Although the causal relationship remains to be elucidated, it is conceivable that the gut microbiome may play a crucial role in RAAS and BP regulation by changing the Th17/Treg cell ratio via SCFAs.

## Compliance with ethical standards

**Conflict of interest** The authors declare no competing interests.

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