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COMMENT

The chicken or the egg: the role of T cell polarity in salt-sensitive hypertension

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Sodium intake is known to increase blood pressure, but there are individuals who do not respond to excessive salt consumption. The problem of salt sensitivity, especially the existence of inverse salt sensitivity, highlights the complex nature of the body's reaction to sodium and has consistently remained a significant research topic in the field of hypertension [1]. One well-established animal model for studying salt-sensitive (SS) hypertension is the Dahl SS rat. These rats demonstrate increased sodium reabsorption due to the hyperactivity of the epithelial Na+ channel (ENaC) in renal tubules. Furthermore, the activity of serum and glucocorticoid-regulated kinase 1 (SGK1), an upstream regulator of ENaC, is also heightened in SS rats [2].

Moreover, immunological mechanism has been also suggested in SS hypertension [3]. In 2010, de Miguel et al. reported that renal infiltration of T lymphocytes increased in Dahl SS rats in relation to the dietary salt intake [4]. Additionally, they found that the elevation of blood pressure was significantly reduced through immunosuppressive treatment. Shortly thereafter, it was demonstrated by Wu et al. that high salt intake induces interleukin (IL)-17 producing helper T cell (Th17) development through the SGK1-dependent pathway [5]. Taking these into consideration, SS individuals can be deemed to be in a pro-inflammatory state. Consequently, the question arises: at which point in the process, from salt loading to ENaC and T-cell activation, should we target therapy?

The present study by Kim et al. offers a significant insight into addressing this question by showcasing the divergent immunological response to a high-salt diet in Dahl SS and salt-resistant (SR) rats [6]. In SS rats, the high-salt diet resulted in an increase in Th17 cells, whereas the same treatment led to a shift towards regulatory helper T cells (Treg) in SR rats. An important point of their study is that there is no difference in baseline T cell polarity between SS and SR rats, and the difference becomes apparent only after salt loading. In other words, T cell polarity is a consequence of the salt sensitivity. In fact, the authors attribute the differential T cell response to salt loading to differences in baseline SGK1 activation (although not included in the main experimental results). Viewed from this perspective, the title of the article "T helper cell polarity determines salt sensitivity and hypertension development" appears somewhat perplexing. Wouldn't it be more appropriate to say that what is happening here is the opposite, namely, that the inherent salt sensitivity determines the polarity of T cell differentiation?

The chicken or the egg dilemma has frequently emerged when discussing the pathophysiology of hypertension [7]. Here, we are left to ponder whether SGK1 or Th17 is the egg that will hatch. Similar to other chicken and egg problems, IL-17 has the capability to enhance the expression of SGK1 [8]. Consequently, these factors create a positive feedback loop, leading to sustained high expression of both IL-17 and SGK1 in developed hypertension. As dendritic cells can sense the extracellular sodium and activate T cell immunity by antigen presentation [9], the onset of salt-induced hypertension becomes more unclear (Fig. 1).

Another important finding in the present study is that SR rat, which is completely protected from sodium-induced hypertension, has significantly higher level of baseline splenic Tregs and serum IL-10 compared to SS rat. In addition, the frequency of Tregs and IL-10 level did not significantly change in response to sodium loading in vivo. Based on these results, one could say that "SR rats are SR because they have higher Tregs". However, SR rats have also been reported to be resistant to angiotensin (Ang) II

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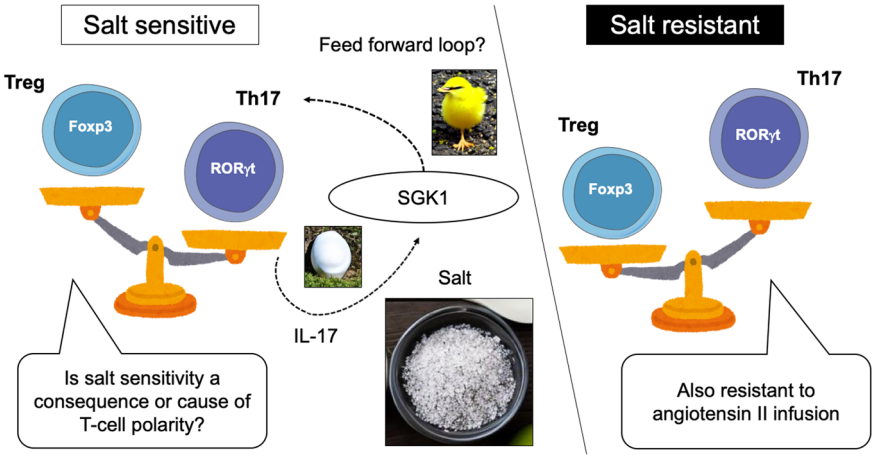

Fig. 1 T helper cell polarity in salt sensitive and salt resistant hypertension. SGK1 activation triggers Th17 cells, potentially establishing a feed-forward loop. However, the precise mechanism that initiates this process remains unclear. The pictures of the chick, egg, and salt were all created using Stable Diffusion. IL-17, interleukin-17; Treg, regulatory T cell; Th17, interleukin-17 producing helper T cell; SGK1, serum and glucocorticoid-regulated kinase 1

administration [10], making them inappropriate for focusing the issue of salt sensitivity.

We know that salt sensitivity reflects sympathetic overactivity. Sympathetic activation usually leads to an upregulation of the renin-angiotensin-aldosterone system (RAAS) in SS hypertension [11], while the plasma renin activity is suppressed due to the systemic sodium retention. What we remember here is that the expression of SGK1 and ENaC is regulated by mineralocorticoid receptor (MR), which is a downstream factor of the RAAS (although the main factor activating MR in SS hypertension may be Rac1 rather than aldosterone). Here, too, we are faced with the chicken and egg problem. Moreover, to go further, it is also known that Th17 is upregulated in Ang II-induced hypertension [12].

The above is just the tip of the iceberg, and there are various other complex elements intricately involved. Therefore, interventional experiments are essential to elucidate the relationship between the egg and the chicken. Although genetic knockout or knockdown in rats is technically challenging, we have the option of denervation as an interventional tool. Since Foss et al. demonstrated SS can be reversed by renal denervation [13], evaluating SGK1 and T cell polarity in this state might provide valuable insights. It is of interest whether different results be obtained when using SS rats compared to what Xiao et al. demonstrated in their Ang II-induced model in 2015 [14].

Given the lack of success in directly targeting the immune system for hypertension treatment, it is crucial to determine the subgroups where currently available medications are most effective. Recently, baxdrostat, a selective inhibitor of aldosterone synthase, has been reported to improve blood pressure control in treatment-resistant hypertension [15]. It is an important research issue for the future to determine whether baxdrostat is beneficial for SS hypertension and whether T cell polarity can be altered by treatment.

In conclusion, the present study conducted by Kim et al. highlights the significant involvement of T cell polarity in the mechanism of salt-sensitive hypertension. Future studies are expected to determine the main cause of salt sensitive hypertension.

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Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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