Cardiovascular Genetics: A News Round-Up

Salt, Immune Function, and the Risk of Autoimmune Diseases

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Study Hypothesis

Autoimmunity has dramatically increased in incidence over recent decades. Studies have shown that a subset of CD4+ T cells, known as interleukin-17 (IL-17)–producing helper T cells (Th17 cells), possess inflammatory properties and promote a variety of autoimmune diseases.1 In the current study, Wu et al2 present evidence that salt induces the differentiation of pathogenic Th17 cells and facilitates the development of autoimmune disease, providing a potential link between increasing salt intake and the rising incidence of autoimmunity.

How Was the Hypothesis Tested?

The authors performed transcriptional profiling of developing Th17 cells to identify potential gene candidates that are involved in regulating Th17 cell differentiation. Further, they conducted a network analysis of the transcriptional changes to identify a promising candidate, serum glucocorticoid kinase 1 (SGK1). The authors assessed the role of SGK1 in Th17 cell differentiation by using SGK1-deficient Sgk1−/− mice and mice lacking SGK1 specifically in IL-17–producing CD4+ T cells (II17f−/−Sgk1−/−) and mice with wild-type (WT) controls. The authors also used SGK1-deficient Cdtf−/−Sgk1−/− mice and II17f−/−Sgk1−/− mice to test the role of Sgk1 in the development of experimental autoimmune encephalomyelitis, a mouse model of multiple sclerosis (an autoimmune disease). Next, the authors performed a network analysis using protein–protein interaction data from public databases to identify downstream effectors of SGK1. To investigate whether salt regulates SGK1 expression and modulates Th17 cell differentiation and the development of autoimmunity in an SGK1-dependent manner, the authors conducted in vitro experiments in which Th17 cells were exposed to increasing salt concentrations as well as in vivo experiments in which SGK1-deficient Cdtf−/−Sgk1−/− mice, with the corresponding WT controls, were subjected to a high-salt diet.

Principal Findings

Transcriptional profiling revealed that SGK1 is expressed in Th17 cells, and its expression showed a strong correlation with IL-23 receptor (IL-23R) signaling and Th17 cell differentiation. Increased expression of IL-23R by the IL-23 cytokine is known to be crucial for maintaining the phenotype of Th17 cells.3 Network analysis with the ANAT software further revealed that SGK1 is the highest ranking node with the largest centrality score, suggesting that SGK1 is a key factor mediating the transcriptional effects of the IL-23R signaling pathway. The authors found that treatment of Th17 cells isolated from Sgk1−/− or II17f−/−Sgk1−/− mice with IL-23 was not able to sustain the Th17 cell phenotype as indicated by impaired production of IL-17. In addition, the authors observed that Cdtf−/−Sgk1−/− and II17f−/−Sgk1−/− mice exhibited a lower incidence of encephalomyelitis as well as reduced severity of the disease compared with controls. These findings suggest the importance of SGK1 in promoting Th17 cell differentiation and in the development of autoimmunity.

Using protein–protein interaction data from multiple databases, the authors identified the transcription factor forkhead box protein 01 (FOXO1) as a possible downstream effector of SGK1. Immunoblot analysis showed that overexpression of SGK1 in WT Th17 cells upregulates the phosphorylation of FOXO1. The phosphorylation of FOXO1 was abolished in Th17 cells isolated from SGK1-deficient Sgk1−/− mice. The authors further demonstrated that the phosphorylation of FOXO1 interferes with its ability to repress retinoic acid receptor–related orphan receptor-γt–mediated Il23r expression, thus leading to increased expression of IL-23R and the maintenance of the Th17 cell phenotype. These results support a model in which SGK1 promotes Th17 cell differentiation via a signaling mechanism that involves the transcriptional factors FOXO1 and retinoic acid receptor–related orphan receptor-γt.

Previous studies have implicated a role for SGK1 in sodium homeostasis.4 Interestingly, the authors reported that culturing WT T cells in the presence of increased salt concentrations upregulated SGK1 expression and promoted Th17 cell differentiation, as indicated by an increase in the mRNA and protein levels of IL-17 and IL-23R. This salt-induced increase in the Th17

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cell phenotype was not observed in T cells isolated from SGK1-deficient Sgk1−/− mice. Moreover, feeding WT or Cd4CreSgk1fl/fl mice a high-salt diet for 3 weeks resulted in a higher frequency of Tn17 cells and the development of more severe encephalomyelitis in the WT mice compared with the SGK1-deficient mice. Taken together, these findings demonstrate that an increased salt concentration promotes Tn17 cell differentiation and the development of autoimmunity in an SGK1-dependent manner.

Implications
This study identifies salt to be a potential novel player in the susceptibility to autoimmune disease by promoting the differentiation of pathogenic Tn17 cells and accelerating the development of autoimmunity in an SGK1-dependent manner. These findings raise the intriguing possibility that high salt levels, especially in the Western diet, may contribute to an increased risk of developing autoimmune disease in humans. Controlled clinical studies in normal population, with high and low-salt dietary challenges to demonstrate induction and inhibition of Tn17 cells, will be of immense interest as a next step to support the provoking findings of the current study.

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Disclosures
None.

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