

INFLAMMATION

Differential effects of salt on immune cell activity

A high-salt diet has been linked to the development of hypertension and cardiovascular disease, and more recently to diseases caused by a disturbance in immune homeostasis, such as rheumatoid arthritis and multiple sclerosis (MS). Now, two studies published in *The Journal of Clinical Investigation* have shed light on the underlying mechanisms that link salt (NaCl) intake to these diseases, by demonstrating differential effects of NaCl on the activation and function of various immune cells.

David Hafler and colleagues previously reported that high NaCl drives an increase in activation of pro-inflammatory type 17 T helper (T_H17) cells. In their latest study, the researchers investigated the effects of high NaCl on regulatory T (T_{REG}) cells, as defects in these cells are a major feature of autoimmune diseases. The effects of NaCl were examined both *ex vivo* and in a humanized mouse model. High NaCl was found to induce IFN γ in T_{REG} cells through serum/glucocorticoid-regulated kinase (SGK1). IFN γ secretion was associated with loss of T_{REG} cell

function, which could be restored upon blockade or knockdown of IFN γ . The researchers propose that these new data provide a mechanistic link between an environmental factor and immune dysregulation in autoimmune disease, and that SGK1 might be a suitable therapeutic target.

“High-salt diets are associated with MS exacerbations, and patients with progressive MS have higher concentrations of NaCl in the central nervous system,” explains Hafler. “Going forward, we have started a clinical trial to determine whether increases or decreases in NaCl intake influence immune system function in patients with MS.”

Previous research from Katrina Binger, Dominik Muller and colleagues also showed that T_H17 cells have boosted activation and function under high NaCl conditions. In their latest study, Binger *et al.* examined whether these findings could be translated to non-inflammatory immune cells. They focused on alternative (M2) macrophages, which are induced by IL-4 and IL-13, and are involved in T_H2 cell-mediated immunity and wound healing.

C57Bl/6 mice were fed a high NaCl diet for 2 weeks and then

injected intraperitoneally with chitin—an M2 macrophage-eliciting molecule. The researchers observed blunted expression of signature genes in macrophages isolated from the peritoneal cavity of these mice. Furthermore, mice on a high-salt diet had a delayed rate of wound healing. The researchers propose that non-inflammatory M2-macrophages have blunted activation and reduced function in response to NaCl, which is in contrast to the stimulatory effects of NaCl on pro-inflammatory T_H17 cells and M1 macrophages.

“When we put all of these studies together, the picture that is emerging is that salt is shifting the balance of the immune system,” proposes Binger. “Salt is increasing the activity of pro-inflammatory cells, and the results from our current study and that of Hernandez *et al.* indicate that salt is also decreasing the activity of non-inflammatory immune cells.”

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ORIGINAL ARTICLES Hernandez, A. L. *et al.* Sodium chloride inhibits the suppressive function of FOXP3⁺ regulatory T cells. *J. Clin. Invest.* doi:10.1172/JCI81151 | Binger, K. J. *et al.* High salt reduces the activation of IL-4- and IL-13-stimulated macrophages. *J. Clin. Invest.* doi:10.1171/JCI80919

