PD Research Round-up: Sodium Sensing: Link to (Auto)immunity

Next to its classical role in hypertension and extracellular fluid volume overload, high salt intake is increasingly considered a key environmental factor that can affect the immune system and, in turn, susceptibility to infections and autoimmune diseases. That potential link has been emphasized by two provocative papers recently published in *Nature* (1,2).

In those studies, Kleinewietfeld *et al.* (1) and Wu *et al.* (2) demonstrated that a high-salt diet can enhance the differentiation of a class of CD4⁺ T helper cells (Th17) that produce interleukin 17 (IL-17). The Th17 cells have been shown to play a role in T cell-mediated tissue injury and the pathogenesis of inflammatory and autoimmune diseases, including inflammatory bowel diseases, multiple sclerosis, and rheumatoid arthritis. The cytokines produced by Th17 cells (IL-17A, IL-17F, and probably others) promote inflammation and enhance secretion of proinflammatory cytokines and chemokines by resident cells, stimulating the infiltration of leukocytes, in particular neutrophils, to the affected tissue (3). The Th17 immune response has also been involved in renal inflammation and glomerulonephritis (3). *In vitro*, the activating effect of high extracellular NaCl concentrations is mediated by the transcription factor NFAT5 (formerly TonEBP, tonicity-responsive binding-protein) and the protein kinase enzymes p38 and SGK1, driving the expression of factors (IL-17A, IL-17F, IL-23 receptor, transcription factor ROR- γ T) that characterize the pathogenic Th17 phenotype. Furthermore, in experimental autoimmune encephalitis, mice on a high-salt diet develop a more severe phenotype, but that exacerbation is prevented in mice lacking SGK1 in their T cells. The authors conclude that a high-salt diet can modulate immunity and may trigger tissue inflammation and autoimmune disorders via the promotion of pathogenic Th17 cells.

NOTES OF CAUTION

Th17 cells have also a protective role, influencing the permeability of the gut and protecting against

extracellular pathogens. Similarly, IL-17 plays an important role in neutrophil recruitment and bacterial clearance during sepsis. Autoimmune diseases are heterogeneous, and the clinical benefit of targeting IL-17 is variable. Many factors influence T helper cells, including nutrients, oxygen tension, and other cytokines (4).

POTENTIAL INTEREST FOR PERITONEAL DIALYSIS

The new data add to previous studies showing that accumulation of NaCl in the interstitium can affect the innate immune system, with activation of NFAT5 in macrophages, resulting in the release of vascular endothelial growth factor C and stimulation of lymphatic vessel growth (5). Similarly, infusion of the peritoneal cavity with saline results in vascular proliferation and increased transport of small solutes (6). We also know that NFAT5 and the conserved kinase p38, which are both centrally involved in the activation of pathogenic Th17 cells, are activated by changes in cellular osmolality. Furthermore, the high-salt conditions used *in vitro* by Kleinewietfeld *et al.* (1) and Wu *et al.* (2) might be encountered *in vivo* (in the interstitium and lymphoid tissue). Taken together, these data suggest that exposure to high NaCl may affect not only peritoneal membrane structure, but also host defense mechanisms and inflammatory changes in the course of peritoneal dialysis.

Olivier Devuyst
Deputy Editor

REFERENCES

1. Kleinewietfeld M, Manzel A, Titze J, Kvakan H, Yosef N, Linker RA, *et al.* Sodium chloride drives autoimmune disease by the induction of pathogenic Th17 cells. *Nature* 2013; 496:518–22.
2. Wu C, Yosef N, Thalhamer T, Zhu C, Xiao S, Kishi Y, *et al.* Induction of pathogenic TH17 cells by inducible salt-sensing kinase SGK1. *Nature* 2013; 496:513–17.

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