264

Inherited salt losing tubulopathies are associated with altered immunity and clinical immunodeficiency due to impaired IL-17 responses

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Introduction
Salt (sodium chloride, NaCl) intake as part of a western diet exceeds the amount with which we evolved. Increased extracellular sodium has been shown to have pro-inflammatory effects on multiple immune cells. This includes IL-17 expressing CD4+ T cells (Th17 cells), which provide protection from mucosal bacterial and fungal infections. Whilst high salt diets have been shown to worsen autoimmune disease in experimental models, the consequences of in vivo salt depletion on immunity are unknown. We therefore investigated immunity in patients with inherited salt losing tubulopathies (SLT).

Methods
Genotyped SLT patients (Bartter syndrome [BS], Gitelman Syndrome [GS], and EAST Syndrome) were recruited from tertiary tubular disorder clinics at 2 centres. A history of clinical features of altered immunity was taken, and compared to healthy and disease controls. Patients underwent ^{23}Na-MRI imaging of the lower limb and immunological investigations. We subsequently assessed the effect of altering extracellular ionic concentrations on IL-17 responses.

Results
47 SLT patients (BS = 23, GS = 22, EAST = 2) were included. Patients were hypokalaemic and hypomagnesaemic with reduced interstitial sodium stores as assessed by ^{23}Na-MRI (Figure 1a and b). SLT patients had clinical features of dysregulated immunity with significantly increased mucosal bacterial and fungal infections, allergic and atopic disease (Table). Aligned with their clinical phenotype, CD4+ subset analysis revealed increased ratio of circulating Th2:Th17 cells, and in vitro Th17 polarisation was reduced in SLT compared to healthy age matched controls (Figure1c). Alterations in STAT1 and STAT3 phosphorylation, the commonest causes of inherited defects in IL-17 responses, were not present in SLT. Calcium flux during T cell activation, which is commonly altered in ion channelopathies leading to immunodeficiency, was also unaffected. We then demonstrated in control cells that additional extracellular sodium (+40mM), potassium (+2mM), or magnesium (+1mM) during T cell activation reduces Th2:Th17 ratio, and augments Th17 polarisation under optimal 7-day culture conditions. Thus, the extracellular ionic environment typical in SLT impairs Th17 polarisation. Finally, in vitro SLT Th17 polarisation could be rescued with the addition of NaCl 40mM to culture conditions. We assessed the intracellular pathway that mediates sodium driven Th17 polarisation, which is dependent on up-regulated serum/glucocorticoid-induced kinase 1 (SGK1) and nuclear factor of activated T cells 5 (NFAT5). Both SGK1 and NFAT5 expression were normal in SLT.

Conclusion
We describe a novel immunodeficiency in SLT patients who have increased bacterial and fungal infections, and reduced Th17 responses. We propose this is due to an altered in vivo ionic environment in SLT, and this study provides new insights into the influence of multiple extracellular ions on T cell polarisation. Whether additional salt supplementation could rescue the immunophenotype in vivo in SLT is unknown.