Nature Reviews Nephrology | Published online 30 Aug 2017; doi:10.1038/nrneph.2017.124

IMMUNOLOGY

The renal sodium gradient in antimicrobial defence

> The heightened medullary sodium concentration ensures local antibacterial defence is at its most efficient

Urinary tract infections are common but rarely extend to the kidneys — an effect that has been attributed, at least in part, to the mechanical consequences of urine flow. New research now shows that the high interstitial sodium concentration in the renal medulla generates a defence zone with enhanced antibacterial immunity against uropathogenic *Escherichia coli* (UPEC). "Our studies show that the high interstitial sodium concentration in the medulla, which is required for the kidney's urine-concentrating function, instructs tubular epithelial cells to produce chemokines that attract monocyte-derived mononuclear phagocytes (MNPs) to the medulla," explains researcher Menna Clatworthy. "This hypersaline environment increases the intrinsic bactericidal and neutrophil chemotactic activities of local MNPs to generate a dynamic zone of defence."

An increasing body of evidence suggests that tissue-resident immune cells, including MNPs, have important roles in a number of diseases; however, the nature of these cells in the kidney is unclear. To characterize the heterogeneity and distribution of MNPs in the kidney, Clatworthy and colleagues studied cells isolated from donated human kidneys that were deemed unsuitable for transplantation. "As we had the whole kidney rather than just biopsy samples containing cortical material, we could properly compare cells in the cortex and medulla," she says. "We were fascinated to find differences in the frequency of MNP subsets in cortex and medulla, and began to pursue the mechanism and functional significance of this finding."

The researchers found higher numbers of $CD14^+$ macrophage-like MNPs within the renal medulla than in the cortex. The medulla is an extremely hypersaline environment and is among the first regions encountered by bacteria ascending from the bladder. The location of these cells, which suggests that they might provide a defence mechanism against infection, prompted Clatworthy and colleagues to assess the efficacy of $CD14^+$ cells against UPEC infection. In line with their hypothesis that the high salt environment of the medulla might enhance $CD14^+$ MNP function, medullary $CD14^+$ MNPs phagocytosed UPEC more effectively than did cortical $CD14^+$ MNPs, and demonstrated enhanced cytokine production in response to UPEC stimulation. Investigation of chemokine profiles within the kidney also showed higher levels of *CX3CL1* and *CCL2* within the medulla than the cortex, consistent with a greater migration of $CD14^+$ MNPs to this region. The secretion of chemokines by renal epithelial cells was stimulated by sodium through a mechanism dependent on the transcription factor NFAT5, and was further enhanced by the presence of *E. coli* lipopolysaccharide. Pharmacological ablation of the renal sodium gradient in mice through administration of tolvaptan or demeclocycline abolished the intrarenal *Ccl2* expression gradient, leading to a reduction in the number of medullary $CD14^+$ MNPs. Importantly, these mice had increased susceptibility to pyelonephritis following intravesical challenge with UPEC with a higher incidence of bacteraemia and death. In line with these findings, kidneys from patients with diabetes insipidus, in whom urine concentration is impaired, also exhibited loss of the cortex–medulla chemokine gradient and reduced expression of medullary $CD14^+$ MNPs, and demonstrated increased bacterial growth from protocol ureteric cultures compared with ureteric cultures from control donors.

The researchers believe that this mechanism provides a way to calibrate tissue defence with the risk of infection. "By utilizing the environmental signal required for urine concentration to generate a defence zone, the immune system reinforces the most vulnerable region of the kidney when it is at greatest risk," explains Clatworthy. "During dehydration, the physical conditions favour infection owing to reduced urine flow, with less mechanical propulsion of bacteria away from the kidney. Our data suggest that, in these conditions, the heightened medullary sodium concentration ensures local antibacterial defence is at its most efficient, revealing a unique mechanism whereby changes in the tissue environment generated by the homeostatic function of the organ stimulate epithelial–MNP crosstalk to optimize tissue defence."

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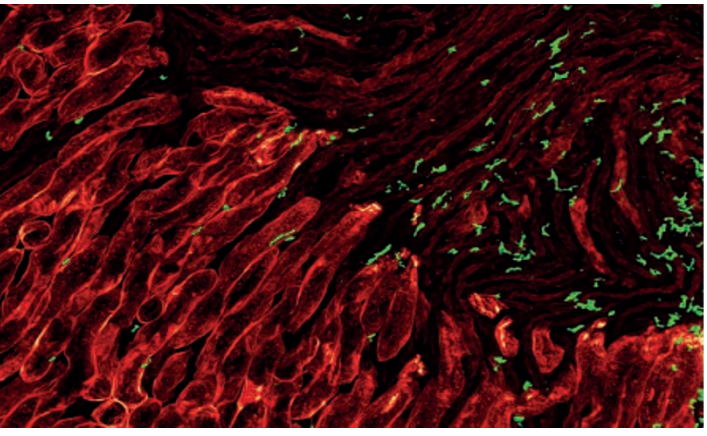

Confocal image showing medullary macrophages (green). Kidney tubules are shown in red. Image courtesy of Menna Clatworthy, University of Cambridge, UK.

ORIGINAL ARTICLE Berry, M. R. *et al.* Renal sodium gradient orchestrates a dynamic antibacterial defense zone. *Cell* http://dx.doi.org/10.1016/j.cell.2017.07.022 (2017)