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AUTOIMMUNE DISEASE

Egress of intestinal T_H17 cells in autoimmune renal disease

Studies over the past few years have revealed a role for type 17 T helper (T_H17) cells in the pathogenesis of several autoimmune diseases, including crescentic glomerulonephritis. These cells are most abundant in the lamina propria of the small intestine under homeostatic conditions; however, they have been observed in kidneys of murine models of crescentic glomerulonephritis where they produce cytokines such as IL-17A, which contribute to renal injury and neutrophil recruitment. Although progress has been made in understanding the effector functions of T_H17 cells in target organs, the origin of these cells remains unclear. New findings demonstrate that T_H17 cells egress from the gut to the kidney in a manner that is dependent on S1P-receptor 1 and CCL20/CCR6 signalling and that depletion of intestinal T_H17 cells ameliorates renal disease. "This finding is of functional relevance, since the absence of intestinal T_H17 cells in germ-free mice and their depletion in mice treated with antibiotics reduces the renal T_H17 response and tissue injury in our model of glomerulonephritis," explains researcher Ulf Panzer. "Oral application of vancomycin is sufficient to reduce the number of intestinal T_H17 cells, as well as T_H17 responses in the kidney, leading to an ameliorated course of crescentic glomerulonephritis without any significant adverse effects, highlighting the great potential of this novel treatment strategy."

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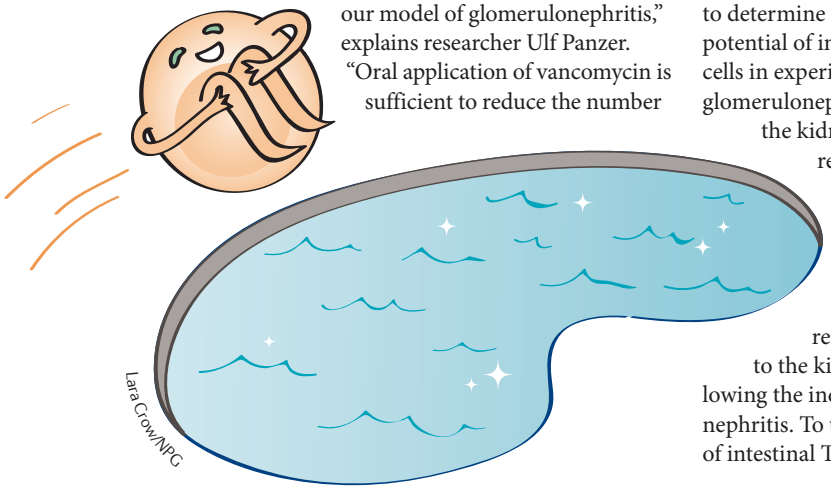
To assess the relationship between microbiota-induced T_H17 cells in the gut and extra-intestinal T_H17 responses in the kidney, Panzer and colleagues first characterized the composition of T-cell subsets in renal biopsy samples from patients with antineutrophil cytoplasmic antibody-associated glomerulonephritis and in mice with experimental nephrotoxic nephritis. "Due to technical limitations, analysis of T_H17 cells in the kidney of patients with glomerulonephritis was not previously possible, but using flow cytometry we identified high frequencies of T_H17 cells in human and mouse crescentic glomerulonephritis," says Panzer. The researchers next performed transfer experiments of renal and intestinal T_H17 cells from *Il17a*-reporter mice into immunodeficient mice to determine the nephritogenic potential of intestinal-derived T_H17 cells in experimental crescentic glomerulonephritis. T_H17 cells from the kidney of nephritic *Il17a*-reporter mice migrated preferentially to the intestine of host mice whereas T_H17 cells from the small intestine of *Il17a*-reporter mice migrated to the kidney of host mice following the induction of nephrotoxic nephritis. To track the migration of intestinal T cells following the induction of glomerulonephritis, the researchers used mice engineered to ubiquitously express Kaede, a photoconvertible protein that changes its fluorescence emission upon photoactivation. "Before our study, only indirect evidence for the involvement of intestinal T_H17 cells in autoimmune diseases was available, but using Kaede-transgenic mice, we directly demonstrate that T_H17 cells from the intestine migrate into the kidney and drive renal tissue injury in crescentic glomerulonephritis," explains Panzer. "We also show that T_H17 cells migrate from the small intestine in a S1P receptor 1-dependent fashion and subsequently migrate into the inflamed kidney via the CCL20/CCR6 axis."

Finally, the researchers demonstrate that depletion of intestinal T_H17 cells in germ-free or antibiotic-treated mice ameliorated renal disease whereas activation of T_H17 cells with *Citrobacter rodentium* led to a more severe renal phenotype. "Our findings have important implications for the mechanistic understanding of how the reservoir of microbiota-induced intestinal T_H17 cells contributes to organ-specific autoimmune disease and for the development of novel treatment strategies in T_H17-driven autoimmune disorders," says Panzer. "Targeting this intestinal T_H17 cell reservoir might present a therapeutic strategy for autoimmune disorders such as crescentic glomerulonephritis."

Susan J. Allison



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