T CELLS

IL-9 breaks down barriers

T helper 9 (T_H9) cells — which are characterized by the production of interleukin-9 (IL-9) and the expression of the transcription factor PU.1 — have previously been shown to contribute to parasitic infection and allergy. Now, a study in *Nature Immunology* implicates T_H9 cell-derived IL-9 in promoting ulcerative colitis by acting on intestinal epithelial cells and impairing intestinal barrier function.

Analysis of the intestinal mucosa from patients with inflammatory bowel disease and control individuals indicated that IL-9 was most highly expressed in the mucosa of patients with active ulcerative colitis. These patients also had high numbers of mucosal T cells that expressed PU.1 and many intestinal epithelial cells that expressed IL-9 receptor (IL-9R).

The association of increased expression of IL-9 and IL-9R with disease was also observed in a mouse model of colitis induced by the hapten oxazolone, which is characterized by ulceration and caused by activated T cells. Using reporter mice, the main source of increased IL-9 expression in mice with oxazolone-induced colitis was shown to be mucosal CD4⁺ T cells. A functional role for these T_H9 cells was supported by the findings that IL-9-deficient mice and mice with a T cell-specific PU.1 deficiency developed less severe oxazolone-induced colitis than control mice.

Next, the authors explored the potential mechanisms for the involvement of T_H9 cells in colitis. Attenuated colitis in IL-9-deficient mice was associated with reduced

production of tumour necrosis factor, interferon- γ and IL-21 by mucosal mononuclear cells, as well as lower levels of T_H2-type cytokines, compared to wild-type mice with colitis. Interestingly, intestinal epithelial cells from IL-9-deficient mice had lower levels of the pore-forming protein claudin 2 (which impairs intestinal barrier function) but higher levels of the tight junction protein occludin and the sealing factor claudin 3 than those of wild-type mice. Conversely, treatment with recombinant IL-9 led to a marked induction of claudin 2 expression in intestinal epithelial cells and suppressed epithelial cell proliferation *in vitro*. Together, this suggests that IL-9 impairs barrier function. Accordingly, the authors detected more translocation of bacteria in the mucosa of wild-type than IL-9-deficient mice with colitis, and this bacterial translocation could be further enhanced by pre-treating wild-type mice with recombinant IL-9.

These findings suggest that IL-9 could be a target for the treatment of ulcerative colitis. Consistent with this, the authors showed that treating wild-type mice with an IL-9-specific antibody 5 days after sensitization with oxazolone reduced disease-associated weight loss and suppressed colitis symptoms over an extended period.

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ORIGINAL RESEARCH PAPER Gerlach, K. et al. T_H9 cells that express the transcription factor PU.1 drive T cell-mediated colitis via IL-9 receptor signaling in intestinal epithelial cells. *Nature Immunol.* <http://dx.doi.org/10.1038/nri.2920> (2014)

“IL-9 could be a target for the treatment of ulcerative colitis”

Andrea Crisante/Alamy