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IMMUNOLOGY

A glia–ILC3 axis

In response to environmental cues, intestinal glial cells secrete factors that alter the function of group 3 innate lymphoid cells (ILC3s), according to new research.

ILC3s are important regulators of mucosal and immune homeostasis in the intestine. These cells are responsive to the local environment, including signals derived from gut microbiota and dietary components, but little is known about the mechanisms underlying their environment-sensing capabilities. "We have shown that haematopoietic stem cells employ neurotrophic factors as survival signals, and that fetal innate lymphoid cells sense micronutrients" explains author Henrique Veiga-Fernandes. "Thus we hypothesized that intestinal ILC3s could interact with the enteric nervous system via neuroregulators."

Neuroregulatory signals include glial-derived neurotophic factor family ligands (GFLs), which bind the RET receptor. In mice, the researchers demonstrated that intestinal ILC3s highly express RET. Deletion of RET in ILC3s markedly reduced ILC3-specific expression of IL-22, which induces epithelial cell reactivity and expression of tissue repair genes. When exposed to dextran sodium sulphate, mice lacking RET in ILC3s showed exacerbated weight loss, colitis and bacterial translocation from the gut, in conjunction with reduced IL-22-producing ILC3s.

After showing that RET-dependent expression of IL-22 in ILC3 is mediated by activation of STAT3, the researchers investigated the source of intestinal GFLs. Notably, ILC3s were found adjacent to projections from glial cells; these cells are known to express GFLs and pattern recognition receptors that sense microbial products. Cultured glial cells were found to be activated by Toll-like receptor ligands, IL-1β and IL-33, and expressed GFLs as a result. Importantly, disruption of the glial cell activation pathway *in vivo* by deletion of *Myd88* in mice suppressed intestinal GFL production and ILC3 expression of IL-22.

"Putative neuroglia–ILC interactions were fully unexplored before this study," says Veiga-Fernandes. "It was a huge surprise!"

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