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MUCOSAL IMMUNOLOGY

Glial cells support ILC3s and gut defence

Group 3 innate lymphoid cells (ILC3s) have a central role in host defence at mucosal sites. In the gut, these cells respond to environmental signals and produce pro-inflammatory and reparatory cytokines, such as interleukin-22 (IL-22). However, the underlying mechanism of environmental sensing by ILC3s remains unclear. A study published in *Nature* now shows that enteric glial cells sense microenvironmental cues and produce neurotrophic factor family ligands (termed GFLs) that act on ILC3s to promote IL-22 production and barrier defence.

Analysis of ILC3s from the gut lamina propria showed that these cells express high levels of the neuroregulatory receptor RET. To explore whether neuroregulators had a role in ILC3 biology, the authors generated RET-deficient chimeric mice and found that, compared with controls, these mice had a specific reduction in the number of IL-22-expressing ILC3s. Conversely, gain-of-function Ret^{MEN2B} mice had increased numbers of enteric IL-22-producing ILC3s. The authors also generated mice in which *Ret* was specifically deleted in ILCs ($Rorgt^{Cre}Ret^{Fl/Fl}$, termed Ret^{Δ} mice) and similarly, IL-22-expressing ILC3 numbers were greatly reduced in these mice.

IL-22 has a central role in maintaining the epithelial barrier, and although untreated Ret^{Δ} mice have normal epithelial morphology, the expression of epithelial defence genes (such as those encoding defensins and mucins) and repair genes was greatly reduced compared with wild-type controls. Furthermore, T cell-deficient Ret^{Δ} mice infected with *Citrobacter rodentium* had a reduced number of IL-22-producing ILC3s and expression of epithelial defence genes, and increased intestinal inflammation, infection burden and mortality compared with littermate controls. Together, these data indicate that ILC3-intrinsic RET signals control IL-22 production and regulate gut defence and repair.

Next, the authors examined the signals that activate ILC3s and found that GFLs induced rapid phosphorylation of the MAP kinase cascade and of signal transducer and activator of transcription 3 (STAT3) in ILC3s in a RET-dependent manner. Furthermore, STAT3 was shown to bind to the *Il22* promoter and induce its transcription. These data confirm a molecular link between RET-dependent ILC3 activation and gut defence through the direct regulation of IL-22.

GFLs are produced by enteric glial cells, suggesting that these cells might integrate commensal and environmental signals to control IL-22 production. Using double ILC3 and glial cell reporter mice, the authors observed stellate-shaped projections of glial cells adjacent to ILC3s within cryptopatches in the gut. Glial cells isolated from the lamina propria produced GFLs in response to Toll-like receptor 2 (TLR2) and TLR4 activation, as well as IL-1β and IL-33 stimulation, and glial cell-derived GFLs promoted IL-22 production by co-cultured ILC3s. Finally, a glial cell-intrinsic deletion of the adaptor molecule *Myd88* in dextran sodium sulfate (DSS)-treated mice resulted in reduced intestinal GFL levels, increased gut inflammation, loss of IL-22-expressing ILC3s and increased weight loss compared with control mice. These mice also had increased susceptibility to *C. rodentium* infection.

Thus, enteric glial cells sense microenvironmental signals via MYD88 to produce neurotrophic factors (GFLs); GFLs then activate ILC3s, via RET, MAP kinase and STAT3 signalling, to induce IL-22 production, which promotes the expression of defence and repair genes in epithelial cells for barrier defence.

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> “a molecular link between RET-dependent ILC3 activation and gut defence through the direct regulation of IL-22”

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