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ILC2s touch a nerve

Three recent papers in *Nature* add to our growing understanding of the neuroimmune interactions that shape host immunity at mucosal tissues. The studies show that mucosal neurons regulate type 2 inflammation by releasing neuromedin U (NMU), a neuropeptide which directly activates group 2 innate lymphoid cells (ILC2s).

Klose *et al.* used immunofluorescence staining to show that ILC2s and T cells co-localize, and appear to make contact, with neurons in the intestinal submucosa. The authors examined ILC expression of neuroactive pathway genes and identified *Nmur1* (which encodes the NMU receptor) as a gene selectively expressed by ILC2s. Subsequent experiments confirmed that NMUR1 is expressed by ILC2s, but not by other immune cells. By contrast, NMU was found to be selectively expressed by cholinergic neurons in the intestine. NMU potently activated ILC2s *in vitro*, inducing their production of IL-5, IL-9 and IL-13 independently of the alarmin IL-33. Furthermore, NMU upregulated ILC2 expression of cell cycle-associated genes and induced their proliferation.

The intestine is highly innervated with NMU^+ neurons, leading Klose *et al.* to explore NMU activity during helminth infection. Intestinal expression of Nmu was upregulated during infection with various helminths and mice treated with NMU showed accelerated expulsion of *Nippostrongylus brasiliensis*. Enhanced worm expulsion was also seen in *N. brasiliensis*-infected lymphocyte-deficient mice reconstituted with wild-type, as opposed to NMUR1-deficient, ILC2 progenitors. Finally, the authors showed that intranasal administration of NMU stimulated cytokine production and proliferation by lung ILC2s and this was associated with increased eosinophilia and mucus production in the airways.

> “mucosal neurons regulate type 2 inflammation”

Similarly to Klose *et al.*, Cardoso *et al.* used transcriptional profiling to identify *Nmur1* as a gene selectively enriched in ILC2s and showed that NMU is selectively produced by cholinergic enteric neurons. They stimulated ILC2s from the intestine or lungs with recombinant mouse peptide NMU (NmU23) and found that this induced ILC2 proliferation and production of IL-5, IL-13, amphiregulin and colony stimulating factor 2. Kinetic analyses showed that NmU23 is a more rapid activator of ILC2s than the alarmins IL-33 and IL-25. Again in agreement with Klose *et al.*, they found that *Nmu* is rapidly upregulated in the lungs and gut during *N. brasiliensis* infection, with NmU23 treatment and NMUR1 expression by ILC2s leading to more rapid worm expulsion in various systems.

In addition, Cardoso *et al.* used neurosphere-derived neuronal organoids to explore how enteric neurons are activated during helminth infection. Stimulating neurons with IL-33 or *N. brasiliensis* excretory or secretory products induced neuronal expression of *Nmu* and this was dependent on the Toll-like receptor (TLR) and IL-33 receptor adaptor MYD88. Enteric neurons are known to express TLRs and the authors showed that mice with a selective deficiency of MYD88 in cholinergic neurons had fewer cytokine-producing ILC2s during *N. brasiliensis* infection.

Wallrapp *et al.* set out to define the transcriptional landscapes seen in lung-resident ILCs at steady state and following activation with alarmins. They found that IL-25 and IL-33 differentially regulate distinct ILC subsets and identified *Nmur1* as a gene that is highly expressed in lung ILC2s at steady state and after IL-25 stimulation, but downregulated in response to IL-33. Similarly to the other studies, Wallrapp *et al.* showed that NMUR1 is predominantly expressed by ILC2s and observed putative ILC2s in close proximity to nerve fibres in the lungs. They also found that neurons in the thoracic dorsal root ganglia express *Nmu*. However, Wallrapp *et al.* reported that NMU only moderately activates ILC2s by itself. Instead, they showed that NMU potently synergizes with IL-25, enhancing cytokine production by ILC2s and allergic airway inflammation, and inducing unique transcriptional programmes in ILC2s.

Taken together, these studies suggest that peripheral neurons can directly sense and respond to alarmins and parasite products to potentiate type 2 immune responses in mucosal tissues. Targeting neuropeptides such as NMU could therefore represent a novel approach for treating allergic inflammation at these sites.

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ORIGINAL ARTICLES Klose, C. S. N. *et al.* The neuropeptide neuromedin U stimulates innate lymphoid cells and type 2 inflammation. *Nature* http://dx.doi.org/10.1038/nature23676 (2017) | Cardoso, V. *et al.* Neuronal regulation of type 2 innate lymphoid cells via neuromedin U. *Nature* http://dx.doi.org/10.1038/nature23469 (2017) | Wallrapp, A. *et al.* The neuropeptide NMU amplifies ILC2-driven allergic lung inflammation. *Nature* http://dx.doi.org/10.1038/nature24029 (2017)