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Neuronal regulation of innate lymphoid cells

Christoph SN Klose[1,2] and David Artis[1]

The cardinal signs of inflammation suggest a close connection between the nervous system and the immune system. However, the cellular and molecular basis of these interactions remains incompletely defined. Recent research has demonstrated that tissue-resident innate lymphoid cells (ILCs) obtain neuronal signals, particularly at mucosal barriers, where ILCs regulate tissue homeostasis. New developments in our understanding of neuronal regulation of ILCs provide insight into how immune responses in tissues are precisely targeted, spatially regulated, and how ILCs sense environmental changes and disturbance of tissue homeostasis. Therefore, neuronal regulation of immune responses is emerging as an important signaling hub for the maintenance of tissue integrity.

Addresses
[1] Jill Roberts Institute for Research in Inflammatory Bowel Disease, Joan and Sanford I. Weill Department of Medicine, Department of Microbiology and Immunology, Weill Cornell Medicine, Cornell University, New York, NY 10021, USA
[2] Department of Microbiology, Infectious Diseases and Immunology, Charité – Universitätsmedizin Berlin, 12203 Berlin, Germany

Corresponding authors:
Klose, Christoph SN (csk2002@med.cornell.edu),
Artis, David (dartis@med.cornell.edu)

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ILCs — what do they see?

In order to maintain tissue homeostasis, both the nervous system and the immune system constantly monitor tissue integrity. However, a full understanding of how these two sensory systems integrate information and coordinate responses remains elusive. The molecular sensors used by the immune cells and neurons are different. Innate myeloid cells recognize conserved pathogen or danger associated molecular patterns through pattern recognition receptors as an indicator of pathogen invasion and tissue disturbance [1]. In contrast, the lymphoid arm of the innate immune system, innate lymphoid cells (ILCs), lack most of pattern recognition receptors [2,3]. Although some reports have documented the expression of toll-like receptors (TLRs) on human ILCs, the recognition of pathogens through pattern recognition receptors is unlikely the dominant mechanism of how ILCs sense their environment [4]. It is well established that ILCs react to alarmins and cytokines such as interleukin (IL)-25, IL-33, thymic stromal lymphopoietin (TSLP), IL-1α, IL-7, IL-23 or IL-15 derived from epithelial cells, stromal cells or other immune cells. In addition, metabolites such as vitamin A or aryl hydrocarbon receptor (AHR) ligands, steroid hormones and inflammatory mediators, such as prostaglandins and resolvins regulate ILC responses [3,5,6]. However, there is a significant gap in knowledge regarding how ILCs as tissue-resident innate lymphocytes detect environmental changes or disturbance of tissue homeostasis and how these immune cells interact with neuronal systems. Recent research has revealed that neuropeptides and neurotransmitters produced by the nervous system shape immune responses in tissues via direct regulation of ILCs [7••,8••,9••,10••,11••,12•,13•]. Since the nervous system and the immune system are the two large sensory units of the body, it is crucial to understand how they exchange information in order to coordinate tissue protective responses. In this review, we will discuss recent advances in understanding of the molecular pathways that regulate bi-directional neuronal-ILC interactions and the implications of these interactions on chronic inflammation and host defense.

What can immune cells learn from neurons?

Despite being two large sensory and effector systems, the organization of the nervous and the immune system is fundamentally different. The nervous system is a network of neurons in relatively fixed positions connected through synapses, which allow direct and stable cell–cell signal transduction. This configuration allows extremely fast, precise and spatial constraint responses using neurotransmitter and neuropeptides, which only act locally and do not diffuse over long distances because they are degraded or absorbed quickly. Although cell-to-cell contact and even immune synapse formation is required for proper immune cell activation, immune cells are mobile and interact with each other through transient cell–cell contact and through cytokines and chemokines which act locally or over some distance [14]. Therefore, due to their different nature, signaling molecules of the nervous system, neuropeptides and neurotransmitters, could enable tissue-resident immune cells such as ILCs to amplify their responses quickly but also constrain local immune responses in tissues, particularly in the context of innate immunity at barrier surfaces.

As close as it gets — co-localization as anatomical basis for neuro–immune interaction at mucosal barriers

ILCs are predominately tissue resident cells localized in various tissues including mucosal barriers such as the intestine and the lung [6,15,16]. Notably, the intestine is densely innervated by the autonomous nervous system, therefore providing opportunity for neuro–immune interaction [17]. The autonomous nervous system consists of the sympathetic nervous system, the parasympathetic nervous system and the enteric nervous system (ENS). Sympathetic and parasympathetic fibers provide extrinsic innervation since their cell bodies are located outside the intestine in the brainstem and spinal cord [17,18]. In addition, the intestine is intrinsically innervated by the neurons whose cell bodies are localized within the intestinal wall, coined the ENS. It should be noted that the ENS with approximately 100 million neurons is the largest accumulation of neurons outside the CNS and is organized in the myenteric and submucosal plexus [19]. The myenteric plexus is localized between the circular and longitudinal muscles, whereas the submucosal plexus lays distal to longitudinal muscles in the intestinal submucosa [17,18].

Immunofluorescent staining has demonstrated that ILC2s are closely entangled with enteric nerves, such as neuromedin U $(NMU)^+$ and tyrosine hydroxylase $(TH)^+$ nerves thus providing an anatomical basis for neuro–immune interaction via short distance mediators, such as neuropeptides and neurotransmitters [7••,8••,10••]. Furthermore, it was reported that projections of $GFAP^+$ enteric glial cells are adjacent to cryptopatches, which are clusters of $CCR6^+$ ILC3s, myeloid cells and B cells [20••]. However, the precise molecular mechanism for neuro–immune interaction remains elusive. It is conceivable that neurons and ILCs form a neuro–immune synapse, but definitive evidence of this is missing so far. In this context, it is unclear whether neuropeptides are released from the neurons synaptically or extrasynaptically, and what the trigger of their release is. It is also possible that some of the neuropeptides are released mainly upon cell damage similar to alarmins released by dying epithelial cells. Therefore, despite their close co-localization, the structural basis of neuro–immune interaction requires further investigation.

Immune regulation by neurotrophic factors

A link between the nervous system and the immune system can be seen early during hematopoiesis in the bone marrow. Mobilization of hematopoietic stem cells (HSCs) is regulated by catecholaminergic neurons [21]. Furthermore, HSCs obtain survival signals through the tyrosine receptor rearranged during transfection (Ret) and the ligand glial cell-derived neurotrophic factor (GDNF) [22]. In addition, polymorphisms in the *Ret* gene and genes involved in Ret signaling are linked to Hirschsprung's disease, which is characterized by a loss of neuronal ganglia in the intestine due to a defect in migration of neural crest cells during fetal development [19,23]. Interestingly, *Ret*-deficient mice not only exhibit defects in the formation of the ENS but also in the formation of Peyer's Patches indicating that the regulatory mechanism that guides neuronal and lymphoid structures have molecular similarities [24,25]. An interaction between neuronal and lymphoid tissue is further supported by the finding that the formation of tertiary lymphoid tissue during intestinal inflammation was dependent on vagal innervation [26]. During fetal development, *Ret* is expressed by hematopoietic lymphoid tissue initiator (LTin) cells, which interact with stromal cells to form Peyer's Patches. Interestingly, stromal cells secreted Ret ligand artemin (ARTN) and this interaction was required for the development of Peyer's Patches [18,24]. Formation of lymphoid structures requires the action of fetal lymphoid tissue inducer (LTi) cells, which lack Ret expression. However, unlike fetal LTi cells, adult $CCR6^+$ LTi-like ILC3s, which mainly reside in cryptopatches in the intestine, are major producers of Ret [6,20••,24]. In the adult intestine, neuronal glial cells, which form contacts with cryptopatches, secrete Ret ligands. Mice with conditional deletion of Ret ($Ror\gamma t^{Cre}$ $Ret^{flox/flox}$) exhibit altered intestinal homeostasis [20••]. In this mouse model, Ret-deficient ILC3s had diminished IL-22 production, and since IL-22 is crucial for barrier immunity, the mice were more susceptible to *Citrobacter rodentium* (*C. rodentium)* infection and DSS-induced colitis [20••,27–29]. Furthermore, conditional deletion of the signaling adapter molecule myeloid differentiation primary response 88 (*Myd88*) in glial cells using $Gfap^{Cre}$ resulted in reduced expression of Ret ligand in glial cells, consequently decreased IL-22 production by ILC3s and increased susceptibility to DSS-induced colitis [20••]. These striking similarities suggest a close association of neuronal and lymphoid cells during the development of lymphoid and neuronal structures, but also for intestinal homeostasis in adult mice.

Neuronal regulation of ILCs

While neuron-associated glial cells and stromal cells are the main source of neurotrophic immune stimulators described above, an array of predominately neuronal-derived stimulatory and inhibitory neuropeptides and neurotransmitters modulate ILC responses. So far, most evidence for neuronal stimulation and inhibition of ILCs comes from studies about ILC2s. A possible proposed explanation is that type 2 immune responses require coordinated action of neurons and immune cells in order to expel parasites or allergens through muscular contractions [30].

Similar to the reported inhibitory effects of vagal nerve-derived acetylcholine on myeloid cells in the cholinergic inflammatory pathway, acetylcholine limits ILC2

responses via the same α7-nicotinic acetylcholine receptor (α7nAChR) expressed on ILC2s [13•,31]. Administration of the α7nAChR agonist dampened allergic lung inflammation in mice via inhibition of ILC2s. Although the source of acetylcholine was not investigated in this study, cholinergic neurons through parasympathetic (vagal) innervation are a potential candidate [13•]. Regulation of myeloid cells by the vagal nerve in models of autoimmunity or infection is well established and referred to as the cholinergic anti-inflammatory pathway [32]. Some of the anti-inflammatory effects mediated by the vagal nerve on myeloid cells might involve ILC3s [33].

Norepinephrine, the signature neurotransmitter of the sympathetic nervous system, is a potent inhibitor of type 2 inflammation as well. Norepinephrine bound to β2 adrenergic receptor (β2AR) expressed on ILC2 and inhibited ILC2 proliferation [10••]. Administration of the β2AR agonist inhibited ILC2 activation and type 2 inflammation in the context of helminth infection and allergic lung inflammation. *Vice versa*, $\beta2AR^{-/-}$ ILC2s were hyper-activated upon *Nippostrongylus brasiliensis* (*N. brasiliensis)* infection resulting in exaggerated type 2 immunity and improved control of helminth infection [10••].

In the intestine, enteric cholinergic neurons express the neuropeptide, neuromedin U (NMU) and form a dense network of NMU^+ neurons, including ganglia in the myenteric and submucosal plexus and nerves fibers reaching the tip of the villi. NMU was upregulated after helminth infection suggesting that infectious stimuli could trigger production of immune effector molecules in neurons [7••,8••]. NMU was shown to be a rapid and potent stimulator of ILC2s, which selectively express Neuromedin U receptor 1 (Nmur1). Administration of NMU stimulated type 2 immune responses *in vivo* and consequently reduced worm burden in wild-type mice, whereas Nmur1-deficient mice were more susceptible to *N. brasiliensis* infection. In addition, NMU promoted type 2 immune responses in the lung during helminth infection and allergic lung inflammation [7••,8••,9••].

Moreover, the neuropeptide vasoactive intestinal peptide (VIP) was found to stimulate ILC2s, which expressed the vasoactive intestinal peptide receptor 2 (VPAC2 or VIPR2) [12•]. VIP is expressed in the ENS but also in neuronal $Nav1.8^+$ nociceptors in the lung. Using the ovalbumin model, Talbot *et al.* found that the crosstalk between these nociceptors and lymphocytes regulated lung inflammation [11••]. Interestingly, capsaicin treatment to stimulate TRPV1 channels increased VIP production and airway inflammation. $Nav1.8^+$ nociceptors not only released VIP to stimulate ILC2s and $CD4^+$ T cells but also responded to IL-5 produced by lymphocytes. In summary, ILCs are major sensors of neuronal factors, and crosstalk between ILCs and neurons, glial cells, and neuroendocrine cells is emerging as a regulator of tissue homeostasis in various disease models (Figure 1).

Neuroendocrine pathways

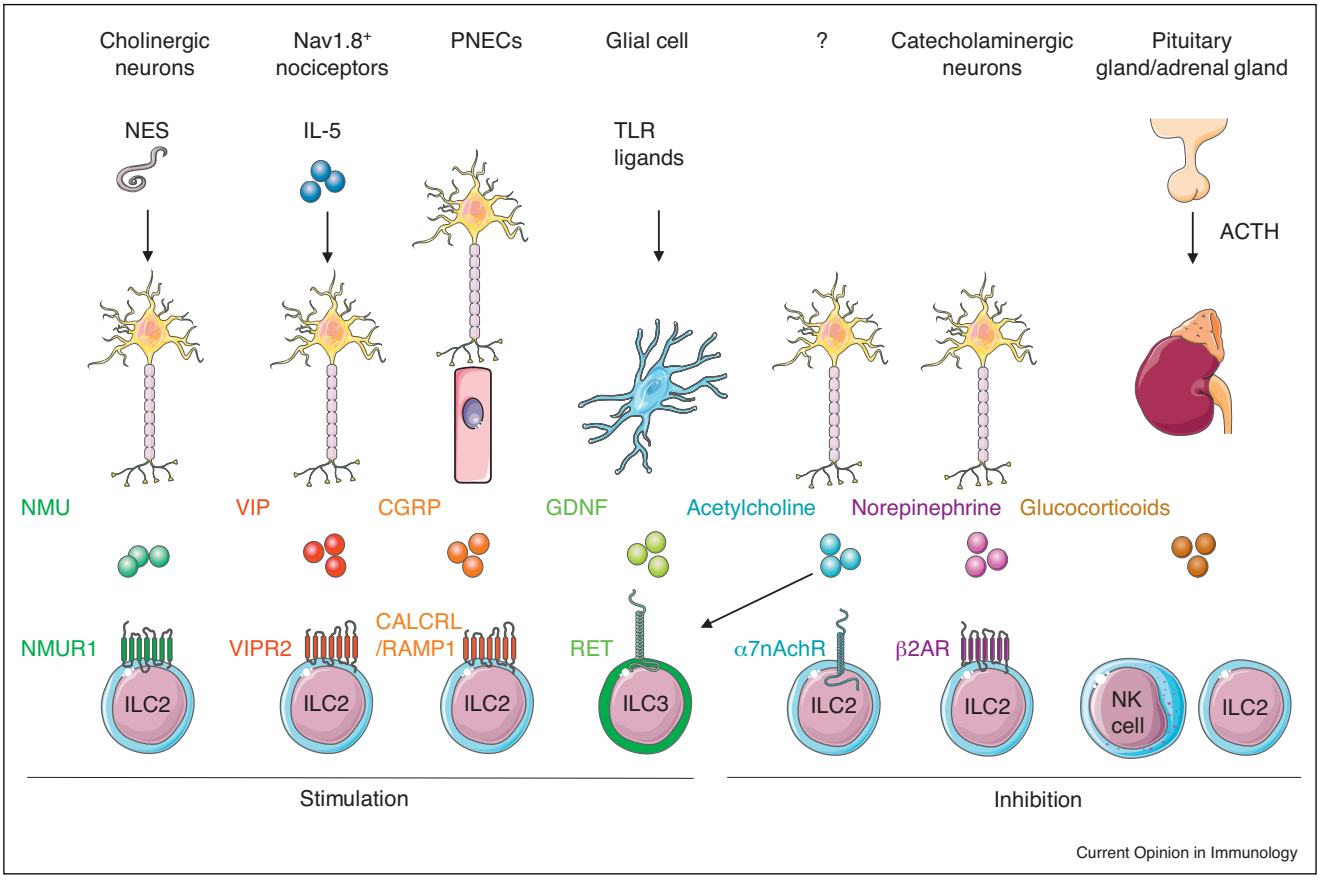
Besides direct neuronal regulation of type 2 inflammation as described above, allergic airway inflammation is regulated by pulmonary neuroendocrine cells (PNECs). PNECs are epithelial airway cells, which store neuropeptides and neurotransmitters in dense core vesicles and form densely innervated cell clusters [34••]. Mice that lacked PNECs due to conditional deletion of the transcription factor *Ascl1* in the airway epithelium developed less airway inflammation and prototypic signs of type 2 immune responses, such as mucus production, when challenged with ovalbumin or house dust mite. Mechanistically, PNECs secreted calcitonin gene-related peptide (CGRP) and gamma-aminobutyric acid (GABA), and ILC2s expressed the CGRP receptors *Calcrl* and *Ramp1* and responded to CGRP stimulation. Interestingly, administration of CGRP and GABA induced airway inflammation in *Acsl1* conditional knockout mice and PNECs were increased in human asthmatic lungs [34••].

Neuroendocrine regulation can be extended to group 1 ILCs, which include conventional NK cells and ILC1s [35,36]. Immediate inflammatory mediators upon LPS challenge such as IL-6, TNF-α and IL-1 are sensed in the hypothalamus and result in activation of the hypothalamus-pituitary-adrenal axis leading to the release of glucocorticoids to limit immune activation , such as occurs in endotoxic shock. Interestingly, specific deletion of the glucocorticoid receptor in group 1 ILCs ($Nkp46^{Cre}$ $Nr3c1^{flox/flox}$) resulted in prolonged IFN-γ production by group 1 ILCs, mainly conventional NK cells, after LPS challenge and decreased IL-10 production by myeloid cells [37•]. The immunosuppressive effects of glucocorticoids are not limited to ILC1s but also control ILC2s during allergic airway inflammation [38,39]. Therefore, neuronal and ILC responses are also indirectly linked through secretion of inflammatory mediators by neuroendocrine cells.

If nerves sense for ILCs, what do nerves see?

Classical sensing of neurons includes chemo sensation, mechano sensation, nociception, thermo sensation and photo sensation mediated by metabotropic G-protein-coupled receptors or ionotropic ions channels [40]. Although the details of how neuronal sensing regulates immune responses are not well understood, a myriad of evidence suggests a strong connection with immune responses. For example, pain sensation is strongly augmented by inflammatory mediators such as prostaglandins, therefore indicating a feedback loop from the immune system to the nervous system [30]. Additional evidence suggests that nerves sense cytokine and inflammatory mediators, especially type 2 cytokines such as IL-4, IL-5, IL-31, TSLP, and histamine, in the development

Figure 1



Regulation of ILC by neuropeptides, neurotransmitters, neurotrophic factors and neuroendocrine circuits.
Release of stimulatory and inhibitory factors by different type of neurons, pulmonary neuroendocrine cells (PNECs), glial cells and adrenal gland is indicated. ILCs express corresponding receptors. NES: *N. brasiliensis* excretory secretory products; ACTH : Adrenocorticotropic hormone.

of allergic airway inflammation and itch [11••,41,42]. Moreover, it appears that chronic inflammation results in permanent and potentially irreversible changes in nerve excitability, providing evidence of bi-directional neuro–immune crosstalk for human health [43].

Regulation of mucosal immune responses by enteric glial cells via TLR — Myd88-dependent pathways is supported by experimental data [20••,44]. Further, some studies even provide evidence that neurons have adopted classical immune sensing strategies, such as direct sensing of pathogen-associated molecular patterns. Expression of pattern recognition receptors TLR 2, 4, and 7 was reported for enteric neurons, and TLR2-deficient mice exhibit altered development of the ENS and secretion of neurotrophic factors [25,44]. Genetic deletion of the signaling adapter molecule *Myd88* abrogated the sensing of *N. brasiliensis* derived excretory-secretory products by enteric neurons and NMU secretion *in vitro* [8••]. Interestingly, NMU was induced during *N. brasiliensis* infection *in vivo*, suggesting that neurons could sense helminth infection and react with the production of neuropeptides [7••,8••]. Deletion of *Myd88* in cholinergic neurons, which express NMU, resulted in curtailed ILC2 responses. Collectively, these data suggest that neurons sense tissue hemostasis and infection not only by classical neuronal perception but also through immune sensing of inflammatory mediators and pathogen-associated molecular patterns. Nevertheless, additional studies using genetic tools to inactivate genes specifically in neurons are required in order to allow definitive conclusions.

Future directions: therapeutic potential of neuro–immune interactions

Since the investigation of neuro–ILC interaction started recently, it is too early to predict if these findings will translate into therapy. However, in light of the findings reviewed here, it is tempting to speculate that some of the drugs already used to treat patients might also affect ILCs [10••,38,39]. For example, β2 receptor agonists are used for treatment of acute exacerbations and together with glucocorticoids for chronic asthma. β2 receptor agonists

operate by relaxing airway smooth muscle during asthma exacerbations [45]. For long-term treatment, it is worth considering that some of the effects might be partially mediated by ILC2s, since it is known that ILC2s correlate with asthma severity. Furthermore, the immunosuppression mediated by glucocorticoids might include effects on ILC2s among many other cells types [38,39].

The therapeutic potential of neuronal regulation of inflammation was already successfully demonstrated by exploiting the cholinergic anti-inflammatory pathway. The cholinergic anti-inflammatory pathway is based on stimulation of the vagal nerve, release of acetylcholine, and other mediators and reduction of inflammatory cytokines such as TNF-α secreted by macrophages in the intestine and spleen of mice [31,32]. Using electronic devices to stimulate the vagus nerve in humans, several studies have demonstrated disease improvement after vagal stimulation in patients suffering from arthritis or asthma [46,47]. Importantly, some of the patients that did not longer respond to conventional anti-inflammatory therapy, such as glucocorticoid treatment, showed improvement upon vagal nerve stimulation [46]. Therefore, a better understanding of the neuronal regulation of immune responses has the potential to be harnessed for therapeutic intervention and improvement of patient care.

Conflict of interest statement

Nothing declared.

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