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Neuro–Immune Cell Units: A New Paradigm in Physiology

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Abstract

The interplay between the immune and nervous systems has been acknowledged in the past, but only more recent studies have started to unravel the cellular and molecular players of such interactions. Mounting evidence indicates that environmental signals are sensed by discrete neuro–immune cell units (NICUs), which represent defined anatomical locations in which immune and neuronal cells colocalize and functionally interact to steer tissue physiology and protection. These units have now been described in multiple tissues throughout the body, including lymphoid organs, adipose tissue, and mucosal barriers. As such, NICUs are emerging as important orchestrators of multiple physiological processes, including hematopoiesis, organogenesis, inflammation, tissue repair, and thermogenesis. In this review we focus on the impact of NICUs in tissue physiology and how this fast-evolving field is driving a paradigm shift in our understanding of immunoregulation and organismal physiology.

1. INTRODUCTION

Organismal physiology and health depend on the coordinated action of multiple cellular networks. A perfect example is provided by the immune system and the nervous system, which harbor myriads of immune and neuronal cell subsets that can sense and respond to multiple environmental conditions and aggressions. Cross talk between the immune and nervous systems has been reported in healthy and disease states, and recent studies indicate that neuro-immune interactions can operate as important immunoregulatory hubs. Notably, immune cells and neuronal cells can colocalize and interact at discrete anatomical sites to drive tissue protection and physiology. These multicellular platforms, known as neuro–immune cell units (NICUs) (1), are challenging our views on how tissue physiology is orchestrated and are likely among the most exciting challenges in immunology over the coming decades.

Neuro-immune interactions are mostly mediated by soluble factors such as neurotransmitters, neuropeptides, and cytokines (2). Immune cells are equipped to respond to neuronal signals by expressing receptors for neuronal cell–derived molecules and, reciprocally, neurons express receptors for immune-derived cytokines and neurotransmitters, which can affect neuronal function (3–5). As such, neuro-immune interactions have been involved in multiple aspects of tissue physiology and have also been described in several conditions, including autism, cancer, multiple sclerosis, and chronic inflammatory disorders (2). Nevertheless, the cellular and molecular fingerprints of NICUs remain poorly understood, but progress in this direction may identify yet unappreciated therapeutic targets.

2. NERVOUS SYSTEM CONSIDERATIONS

Neuro-immune interactions can operate in the central nervous system (CNS) and in the peripheral nervous system. The latter comprises neurons and glial cells organized in nerve bundles, coming from the CNS. Immune responses have been shown to be modulated by the peripheral nervous system, notably by the autonomic nervous system, but also by sensory and motor nervous system inputs (6).

The autonomic nervous system can be classified into (*a*) the sympathetic nervous system (SNS), (*b*) the parasympathetic nervous system (PaNS), and (*c*) the enteric nervous system (ENS). Sympathetic nerves emerge from the thoracolumbar spinal cord and produce catecholamines (**Figure 1**). SNS stimulation was shown to impact a wide range of immune parameters, including function, survival, proliferation, circulation, and trafficking of immune cells (5). Adrenergic receptors targeted by catecholamines are expressed by immune cells, and their stimulation regulates expression of receptors and cytokines essential for coordinated immune responses (7). PaNS neurons emerge from the cranial nerves and the sacral spinal cord and regulate involuntary responses at resting states (**Figure 1**). However, the extent to which PaNS cholinergic neurons regulate immunity remains unresolved, since it is still unclear which lymphoid organs are innervated by the PaNS. The cell bodies of the ENS are localized within the walls of the gastrointestinal tract, in contrast to the SNS and PaNS cell bodies that are found in the spinal cord ganglia (2) (**Figure 1**).

Finally, neuro-immune interactions can also be established at a systemic level, whereby neurotransmitters and hormones can be released into circulation from the CNS in response to environmental stimuli. Reciprocally, systemic and peripheral release of immune-derived cytokines can regulate neuronal functions as discussed further below (6, 7).

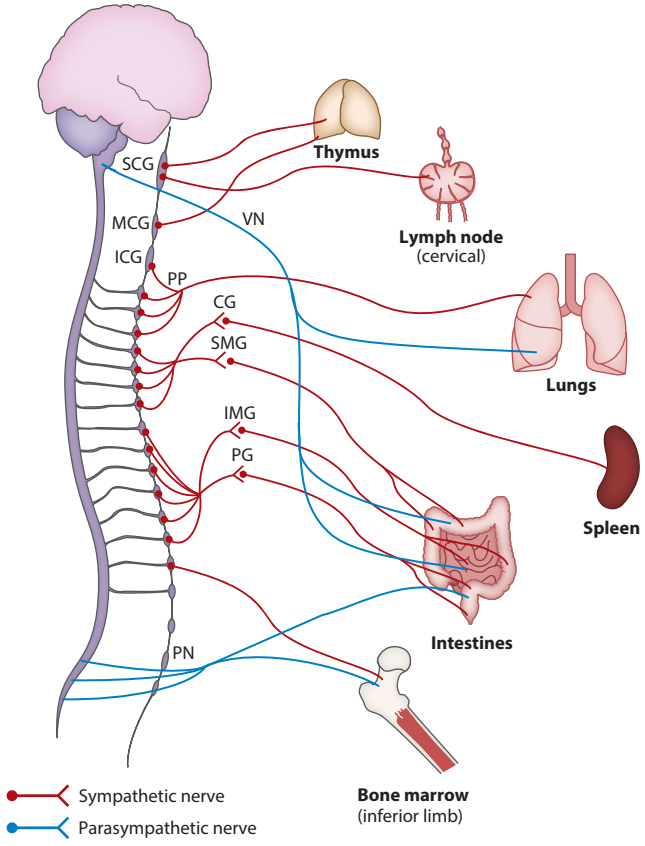

Figure 1

Lymphoid tissue and mucosal innervation. The major autonomic pathways that innervate lymphoid organs and mucosae are illustrated. These include two branches of the autonomic nervous system: the SNS (*red*) and the PaSNS (*blue*). The SNS circuit is a two-neuron chain with preganglionic sympathetic neurons innervating postganglionic neurons whose nerve endings reach target organs. The PaSNS is also a two-neuron chain of efferent nerves with preganglionic neurons in the CNS that end upon postganglionic neurons in the organs they supply. Abbreviations: CG, celiac ganglia; ICG, inferior cervical ganglia; IMG, inferior mesenteric ganglia; MCG, medial cervical ganglia; PaSNS, parasympathetic nervous system; PG, pelvic ganglia; PN, pelvic nerve; PP, pulmonary plexus; SCG, superior cervical ganglia; SMG, superior mesenteric ganglia; SNS, sympathetic nervous system; VN, vagus nerve. This figure was modified from Servier Medical Art, licensed under a Creative Commons Attribution 3.0 Generic License. **https://smart.servier.com/**.

3. TISSUE INNERVATION AND IMMUNE REGULATION

3.1. Neuronal Control of Hematopoiesis

Immune cells originate from hematopoietic stem cells (HSCs) through a developmentally regulated process that gives rise to all blood cell lineages: hematopoiesis (8). In adult mammals, hematopoiesis mostly takes place in the bone marrow, whereas T lymphocyte development occurs in the thymus. Innervation of the bone marrow by the autonomic nervous system regulates the development of new lymphoid and myeloid cells (9). Early evidence for innervation of the bone marrow was provided by the histological studies of Calvo (10) in 1968, when he postulated

the control of bone marrow function by autonomic and sensory neurons. Sympathetic nerve fibers are the most important neuronal inputs in the bone marrow (**Figure 1**). While the periosteal bone region is the most densely innervated, when total volume is considered it is the bone marrow that receives most SNS innervation (11–13). Sympathetic nerves and stromal cells form neuroreticular complexes present in hematopoietic niches, where HSCs are maintained and differentiate (14–16). One example of neuronal-hematopoietic regulation is the circadian mobilization of HSCs to the bloodstream. In this process, catecholamines suppress stromal cell niche functions, increasing the egress of hematopoietic cells from the bone marrow. Notably, circadian oscillations of bone marrow noradrenaline induce rhythmic expression of CXCL12 by mesenchymal stem and progenitor cells leading to the rhythmic release of HSCs (17, 18). More recently, it was found that bone marrow innervation by the SNS declines with age and this reduction leads to the aging of HSCs (19). Interestingly, the decline in regenerative capacity and differentiation potential of aged HSCs critically relies on the loss of SNS nerves or adrenoreceptor β_3 signaling in the hematopoietic niche (19). Sympathetic signals are also critical regulators of hematopoietic regeneration following exposure to cytotoxic drugs or irradiation. Sympathetic neuropathy leads to hematopoietic exhaustion, which can be rescued by administration of neuroprotective agents (20). Furthermore, sympathetic neuropathy is present in acute and chronic myeloid leukemia, and these neuronal defects can enhance leukemia malignancy by altering mesenchymal niche activities and expansion of malignant HSCs (20, 21). Finally, SNS-derived neuropeptide Y also promotes the release of HSCs from their niche through the activation of matrix metalloproteinase 9 (22–24), while substance P and neurokinin A stimulate stromal cells to produce hematopoietic cytokines (25).

As for the PaNS, despite some evidence for the presence of cholinergic nerve fibers at hematopoietic sites (**Figure 1**), little is known of its role in hematopoiesis (26). In a recent study, Pierce et al. (27) showed that expression of muscarinic receptor type 1 (CHRM1) in the CNS controls HSC release from the bone marrow via release of glucocorticoids from the hypothalamic-pituitary-adrenal axis and not from local parasympathetic nerves. Sensory peptidergic innervation is also found in the bone marrow. Sensory nerves reach the bone marrow through perivascular plexuses and feed back to autonomic control centers in the spinal cord regulating sympathetic tone through intraspinal reflex arches (28). Sensory neurons produce neuropeptide Y, substance P, vasoactive intestinal peptide (VIP), and calcitonin gene–related peptide (CGRP) (6, 12, 28, 29). Importantly, ablation of these nerves reduces blood cell counts and bone marrow cellular density, and in vitro stimulation of HSCs with sensory nerve–derived neuropeptides stimulates progenitor activity (28). Overall, release of neuropeptides from sensory nerve terminals in the bone marrow appears to have a positive stimulatory effect on HSC activity and hematopoiesis (11, 30–32).

Schwann cells, a special type of glial cells that ensheathe nerves within the bone marrow, can also control HSC quiescence through activation of latent TGF-β (33). Glial cell–derived neurotrophic factor (GDNF) family ligands also regulate hematopoiesis since ablation of their receptor in hematopoietic cells impairs survival of HSCs. Notably, activation of the GDNF family ligand receptor RET provides HSCs with critical *Bcl2* and *Bcl2l1* surviving cues, which are essential for cell-autonomous stress response and reconstitution potential (34).

The presence of catecholamines in the mammalian thymus was first demonstrated in 1974 (35). It is now well established that sympathetic nerve fibers innervate the thymus. Notably, thymic sympathetic nerves originate in the superior cervical and stellate ganglia, both belonging to the upper paravertebral ganglia of the sympathetic chain (36) (**Figure 1**). SNS fibers enter the thymic cortical regions through the thymic capsule alongside blood vessels, and these fibers are predominantly found in the cortex, especially in the corticomedullary junction (37). Sympathetic neurons are found in close proximity to thymocytes, thymic epithelial cells, mast cells, and macrophages (6). These neuronal cells express catecholamine receptors and tyrosine hydroxylase; thus, they produce

norepinephrine (38). Catecholamines were shown to have an inhibitory action on thymopoiesis (6, 39). Similar to the bone marrow, sympathetic innervation changes with age-related thymic involution (40). During thymic involution, the density of nerve fibers and the norepinephrine concentration increase, suggesting a role for sympathetic innervation in age-associated immune deregulation (41).

Thymic PaNS innervation was initially identified by histochemical and immunocytochemical studies of choline acetyl transferase, revealing positive nerve fibers around blood vessels in the thymic parenchyma (38) (**Figure 1**). Nevertheless, the functional relevance of these PaNS fibers remains mostly unexplored. More recently, nonmyelinating Schwann cells were found to form a network in all thymic compartments, and these glial cells closely associate with blood vessels, dendritic cells (DCs), and lymphocytes (42).

3.2. Neuronal Inputs in Secondary Lymphoid Organs

Autonomic innervation of the spleen is exclusively provided by the splenic nerve, which comprises SNS fibers from the superior mesenteric-celiac ganglion (**Figure 1**). The sympathetic circuit to the spleen also includes preganglionic cholinergic sympathetic neurons that innervate postganglionic neurons (43). Postganglionic nerve terminals reach the spleen alongside blood vessels, forming a substantial network in the white pulp, becoming less dense in the red pulp and in B cell follicles (44). Nerve terminals in the splenic parafollicular zones are found in the vicinity of T cells, macrophages, and B cells (45).

The impact of splenic sympathetic innervation has been extensively explored. It is mainly regulated by norepinephrine, and it has been named the inflammatory reflex (46). The splenic inflammatory reflex is controlled by noradrenergic and cholinergic neuronal inputs, which result in attenuated activation of splenic macrophages (47). While there is no direct parasympathetic innervation in the spleen (43, 47), the splenic sympathetic tone can be controlled by the vagus nerve (48). This was termed the cholinergic anti-inflammatory pathway, since stimulation of the vagus nerve was shown to inhibit tumor necrosis factor (TNF) in inflammatory settings (49). In contrast, vagotomy significantly increases systemic TNF levels in response to intravenous endotoxin (50). Vagal regulation of splenic immunity was shown to be indirect, as it relies on the migration of vagus-primed immune cells from the gut to the spleen (50–52). A more controversial hypothesis is that vagal nerve inputs activate sympathetic neurons in the celiac ganglion (52, 53). Nevertheless, it is generally accepted that the cholinergic anti-inflammatory pathway leads to increased splenic norepinephrine (7, 54, 55).

Neuropeptides produced by sympathetic and sensory neurons are also relevant in the context of splenic immune regulation. Neuropeptide Y controls effector T and B cell expansion and IgG2a production (56, 57). Sympathetic cell– and T cell–derived VIP downregulates proinflammatory cytokine production by macrophages and T cells and activates tolerogenic DCs, leading to generation of regulatory T cells (Tregs) (58, 59). Sensory neuron–derived substance P stimulates lymphocyte proliferation through induction of IL-2, IL-4, and IFN-γ (60). Substance P also acts as a proinflammatory signal by inducing granulocyte- and macrophage-derived proinflammatory cytokines (60, 61). Sensory neuron–derived CGRP downregulates inflammation by acting on DCs, T cells, macrophages, and neutrophils (62–64). Finally, neuronal regulation of the spleen is also mediated by systemic neural and endocrine mediators found in the bloodstream (7).

The anatomical origin of lymph node innervation has been less explored when compared with the spleen counterpart, but it is likely to be region specific. For example, SNS fibers in cervical lymph nodes originate from the superior cervical ganglia (65) (**Figure 1**). Sympathetic nerve fibers enter lymph nodes alongside blood vessels into the subcapsular plexus (65). From

the medulla to the paracortical regions, SNS fibers continue along blood vessels into T cell zones. In contrast, SNS fibers are not found in the nodular regions and germinal centers (13, 66). Norepinephrine release in lymph nodes is essential for antigen processing and efflux of activated lymphocytes into circulation, and the effect of catecholamines is dependent on the timing of their release in relation to other neuron-derived molecules (67). Without norepinephrine, cytotoxic T lymphocyte activation is reduced, while type 2 T helper (Th2) cell responses are unperturbed (13, 67–69). Substance P– and CGRP-producing nerve fibers have been detected in the vicinity of lymph node lymphocytes despite lack of evidence for lymph node cholinergic fibers (6). Finally, neuronal innervation contributes to lymph node development during embryogenesis. Notably, motor neuron–derived retinoic acid seemingly activates stromal cells that sequentially attract lymphoid tissue–inducer cells (70, 71).

Peyer patches are located in the antimesenteric side of the small intestine, and similar to lymph nodes they have organized T and B cell zones. Peyer patch development requires recruitment of hematopoietic cells to the gut and depends on neuroregulatory signals (71). Notably, expression of the neuroregulator RET in $CD11c^+$ lymphoid tissue initiator cells is required for Peyer patch organogenesis (72). RET signaling in *trans* occurs in these cells through the GFRα3 (GDNF family receptor alpha) RET coreceptor and the glial cell–derived neurotrophic factor Artemin (72, 73). Interestingly, RET signals in *cis* are essential for ENS formation, via GFRα1 and the GDNF (72, 73). Thus, differential RET signaling pathways drive development of the enteric lymphoid and nervous systems. This solidifies the hypothesis that the immune and nervous systems may have evolved to integrate common signals that are essential for their development and function (1, 74, 75).

3.3. Neuronal Inputs in the Intestine

Intestinal neurons can be classified as intrinsic (cell bodies are found within the gut: ENS) and extrinsic (cell bodies located outside the intestine: sympathetic and parasympathetic autonomic nervous system).

3.3.1. The enteric nervous system. The adult intestine contains the largest immune cell compartment in the body and a neural network with as many neurons as the spinal cord. There are millions of enteric neurons, and thus the term second brain was coined (76). ENS neurons are intrinsic, since their cell bodies are within the walls of the gastrointestinal tract. Enteric neuronal networks are organized into the myenteric (or Auerbach) plexus and the inner submucosal (or Meissner) plexus, forming two layers of interconnected ganglia (77). Submucosal neurons control gut secretions, nutrient absorption, and local blood flow, while neurons in the myenteric plexus coordinate smooth muscle contractions (77, 78). A network of millions of enteric sensory neurons, interneurons, and motor neurons is able to produce panoplies of neurotransmitters and neuropeptides (2, 77, 79). The ENS is derived from multipotent neural crest cells that during embryonic development give rise to neurons and glial cells (77). However, neurogenesis and gliogenesis also occur postnatally (80).

Enteric glial cells are found in enteric ganglia, within interganglionic tracts, in the smooth muscle, and in the lamina propria. In the lamina propria, glial cells and neuronal projections form a continuous network that extends from the base of the crypts to the mucosa. This neuronal network localizes in close proximity to subepithelial myofibroblasts, the epithelial membrane, and lymphatic vessels (81). Intestinal glial cells outnumber enteric neurons and can be identified by the expression of p75, Sox-10, GFAP, and S100β (82). Early studies indicated that glial cell ablation leads to complete disruption of intestinal barrier integrity, resulting in fatal jejunoileitis (83, 84). However, recent studies where partial conditional ablation of enteric glial cells was performed

failed to induce intestinal inflammation and disrupted intestinal barrier (85). Interestingly, enteric glial cells were shown to express MHC-II molecules in the inflamed ileum of Crohn disease patients, suggesting that glial cells have critical roles in this condition (86, 87). In line with this idea, enteric glial cells were shown to sense pathogens and to produce neurotrophic factors that stimulate protective immune responses and help maintain the epithelial barrier integrity (88–92). Finally, enteric glial cells can transdifferentiate into enteric neurons upon damage-induced neuronal loss (74, 93).

The maintenance of gut homeostasis depends on the coordinated development and response of the ENS and the intestinal immune systems (74, 77, 80). As previously discussed, the most notable example is the coordinated development of Peyer patches and ENS via RET signals (72, 73, 94). Similarly, the development of fetal lymphoid tissue–inducer cells depends on retinoic acid that may be supplied by local enteric neurons (70, 95).

3.3.2. Sympathetic inputs in the intestine. Intestinal peripheral nervous system neurons provide an axis between the CNS and the intestine, and this communication route has been termed the gut-brain axis. Sympathetic innervation of the gut is achieved by norepinephrine-producing efferent neurons extrinsic to the ENS (96, 97) (**Figure 1**). SNS nerve terminals densely innervate the intestine in contact with the serosa, mucosa, muscularis, and myenteric plexus neurons (98–100). Sympathetic signals were shown to regulate intestinal immune responses through norepinephrine release, and adrenergic receptors are expressed by most innate and adaptive immune cell populations (101). Sympathetic neurons are present in Peyer patches, where they are found in close proximity to DCs, plasma cells, and T cell zones. Norepinephrine stimulates cytokine production by T cells, B cell proliferation, and immunoglobulin secretion (102, 103). In the muscularis, interactions between intestinal macrophages and sympathetic varicosities suppress TNF-α secretion and phagocytosis (104). The SNS is also involved in intestinal pathologies. Activation of the sympathetic reflex by inflammatory molecules leads to impaired gastrointestinal motility and modulates the intestinal immune system in conditions such as postoperative ileus, intestinal parasitic infection, and experimental colitis models (96). Crohn disease patients also have altered sympathetic innervation (105). Reciprocally, inflammation also impacts sympathetic nerves by inducing sprouting of fibers surrounding sensory neurons of the dorsal root ganglia, contributing to visceral hypersensitivity in inflammatory bowel diseases (106, 107).

3.3.3. Parasympathetic inputs in the intestine. Parasympathetic innervation in the gut is a two-neuron chain, with pre- and postganglionic neurons. Efferent neurons reach the midgut coming from the vagal dorsal nucleus, while efferent neurons reach the distal colon via the sacral spinal nerves (108) (**Figure 1**). The vagus nerve also plays a role in gut immunomodulation establishing connections with the ENS in the intestinal myenteric plexus (109). Vagal nerve activation of enteric glia enhances barrier function through nicotinic acetylcholine receptor (nAChR) signaling (109). By controlling the inflammatory reflex, vagal innervation can also inhibit enteric innate immune responses (109). Parasympathetic inputs also modulate intestinal immunity through secretion of neuropeptides and stimulation of the hypothalamic-pituitary-adrenal axis (2).

3.4. Neuronal Inputs in the Lung

The respiratory and gastrointestinal tracts have many structural similarities: an extensive luminal surface, an epithelial barrier, and an overlying mucous layer, which provide a barrier for commensals, pathogens, and foreign antigens. A dense network of pulmonary nerve fibers is found throughout the parenchyma of the respiratory system. Innervation of the airways is associated

with glands, epithelial barrier, smooth muscle, and vasculature. There are even a small number of intrinsic neuronal ganglia in the lung that, akin to those of the ENS, derive from neural crest cells (110, 111). Efferent innervation of the airways comes from sympathetic and parasympathetic postganglionic nerve fibers (**Figure 1**). These nerve fibers are involved in the regulation of mucous gland secretion, airway tone, and vascular smooth muscle tone (112). Sympathetic innervation comes from the superior cervical and stellate sympathetic ganglia, while parasympathetic innervation originates in the nucleus ambiguus in the brainstem, with a small number of neurons coming from the vagus nerve (**Figure 1**) (113, 114). Sympathetic nerve fibers are characterized by the expression of tyrosine hydroxylase, neuropeptide Y, nitric oxide synthase, VIP, and ATP (112, 115), and adrenergic receptor stimulation through norepinephrine modulates pulmonary immune function (101). Curiously, and in contrast to other mammals, sympathetic innervation of smooth muscle in humans is almost absent, and regulation of bronchial tone mostly relies on circulating catecholamines (116).

Pulmonary parasympathetic neurons can be classified into two main populations, classic cholinergic neurons in the airway walls and noncholinergic postganglionic neurons (112, 117). The main function of pulmonary cholinergic neurons is the induction of smooth muscle contraction and consequent bronchoconstriction (117). Noncholinergic postganglionic neurons originate in the myenteric plexus of the esophagus and in the outer striated longitudinal muscle layers (118). Acetylcholine signals through muscarinic receptors and nAChRs in immune cells. Similar to the case of other organ systems, in the airways, muscarinic receptor activation has proinflammatory effects while nAChR signaling has anti-inflammatory effects (112, 117). Parasympathetic neurons also release nitric oxide and VIP, which induce airway smooth muscle relaxation (115). Acute and chronic inflammatory respiratory diseases were shown to be modulated by immune and nervous system inputs. PaNS activation is a major source of lung inflammation in viral and bacterial infections, allergic asthma, and chronic obstructive pulmonary disease. Notably, vagal efferent and afferent neurons control symptoms such as bronchospasm, cough, dyspnea, and airway hyperreactivity (119).

Lung sensory neurons originate in the vagus nerve and lower cervical and upper thoracic spinal dorsal root ganglia (112, 113). Sensory innervation is essential for the pulmonary cycle, bronchomotor and vasomotor tones, and mucus secretion (112, 120). Sensory nerves also initiate respiratory sensations and reflexes (coughing and sneezing) in pathologic conditions (112). Additionally, there is evidence for the control of inflammation by peptidergic sensory neurons. For example, during viral infection, increased activity in sensory and autonomic innervation leads to the urge to cough (120). Nociceptor activation was also shown to induce the release of neuropeptides involved in recruitment and activation of immune cells (64, 121). In line with these findings, asthma patients have increased length and number of sensory nerves, which are also more sensitive to inflammatory stimuli (115, 122, 123). Thus, airway inflammation induces release of neuropeptides by sensory neurons, and this promotes sustained proinflammatory responses. Nevertheless, in humans the effect of neuropeptides on airway inflammation remains elusive since human sensory nerves have low expression of neuropeptides (124, 125).

4. IMMUNE-DERIVED SIGNALS AND NERVOUS SYSTEM FUNCTION

Neuroimmune interactions are bidirectional, and immune-derived cues can signal to neurons. Immune cells produce cytokines; neuropeptides, such as enkephalins and endorphins; neurotransmitters, such as norepinephrine and acetylcholine; and hormones, such as luteinizing hormone and prolactin (126). Release of these molecules by immune cells has a significant impact in the nervous system. A notable example is the production of bone morphogenetic protein 2 (BMP2) by enteric macrophages, which stimulates expression of colony stimulatory factor 1 (CSF1) by neurons. This cross talk leads to an increase in peristaltic contractions and macrophage proliferation

(127). The role of T cell–derived cytokines in neurons is also nicely illustrated by the finding that type 2 cytokines can induce chronic itch via sensory neuron activation in the skin (157).

One of the most relevant pathways of neuroimmune cross talk is the gut-brain axis. The enteric immune system can communicate directly and indirectly with the CNS to fine-tune responses to pathogens and tissue damage. The indirect route is mediated by the release of cytokines into circulation. Cytokines can reach the brain and activate neurons at circumventricular organs or can be actively transported to other brain regions (44). One example is the role of TNF and TNF-family cytokines in nervous system development and function (128–130). The direct route of gut-brain communication involves vagus nerve afferents and visceral afferents, which convey local immune signals to the brain (78, 109). Gut-brain communication modulates sympathetic input to immune organs. SNS cues can fine-tune immune responses, notably by modulating blood flow and cell distribution, but the SNS itself is also a target of immune-derived molecules. For example, the inflammatory molecule IL-1 increases circulating corticosteroids, which in turn promote the turnover of norepinephrine by hypothalamic noradrenergic neurons, thus resulting in a decrease of norepinephrine in the spleen (131, 132). However, the exact mechanisms behind the gut-brain axis have not yet been fully unraveled, in particular the CNS pathways that influence sympathetic outflow (132). Sympathetic deregulation can also lead to immune pathologies and vice versa. For example, human inflammatory conditions and mouse models of lupus present sympathetic neuropathy (133). In humans, high SNS activation or sympathetic neuropathy can be found in patients with diabetes, lupus, rheumatoid arthritis, heart failure, and chronic obstructive pulmonary disease (134–137). However, SNS regulation is only one dimension of the complex gut-brain axis. Enteric glial cells also seem to be involved in CNS disorders. Indeed, in transmissible spongiform encephalopathy, enteric glial cells act as a reservoir of infective prions serving as a template for misfolding proteins that then travel to the brain through autonomic pathways (138–140). Glial cells are also involved in the gut-brain axis in Parkinson disease, where enteric neurons and glial cells exhibit pathological features of Parkinson disease (141, 142).

Another pathway of neuroimmune cross talk is the central reflex activity caused by lung inflammation. Sensory neurons can sense stimuli that are conveyed to the nucleus tractus solitarius in the brain through the afferent vagus nerve (117). Activation of sensory lung neurons leads to neuropeptide production that activates central reflexes such as cough. Central reflexes are immune dependent, since inflammation can modulate the activation of sensory neurons (118). Nociceptors can also be activated by proinflammatory cytokines and communicate these signals to the brain (143). For example, IL-5 stimulates sensory neurons expressing IL-5Ra to produce VIP (144). Thus, lung vagal afferent neurons play an important role during lung infection and inflammation, through the pulmonary vagal inflammatory reflex.

Aberrant immune responses can also affect neuronal function and behavior. A canonical example is the impact of infection on behavior. During infection, systemic proinflammatory cytokines reach a threshold where mammals develop symptoms such as fever, lethargy, anorexia, and social isolation. These sickness-induced behavioral changes allow the body to recover without spreading infection and limit inflammatory tissue damage (145). While behavioral changes during disease are mediated mostly by circulating proinflammatory cytokines, we cannot ignore the role of CNS immune cells. Microglia, brain-resident macrophages, are involved in neuronal regulation and consequently in pathological processes of many neurological diseases (146). The CNS immune repertoire is limited, but meningeal immune cells can cross the blood-brain barrier, and the release of cytokines in the brain can have profound impacts on behavior. For example, IFN-γ controls neural connectivity and can induce changes in social behavior through signaling in prefrontal cortex neurons (147). Another cytokine that impacts behavior is IL-17, which during fetal development regulates neuronal function and is involved in autism spectrum disorders, schizophrenia,

and multiple sclerosis (148, 149). Meningeal IL-4-producing T cells have also been implicated in learning and memory (150). More recently, a new study has placed B lymphocytes as important regulators of oligodendrocyte proliferation and neuron myelination during early development, suggesting that B cell dysfunction may also contribute to mental disorders (151).

5. NEURO–IMMUNE CELL UNITS

5.1. Neuron-Neutrophil Interactions

Neutrophils provide a first line of host defense against tissue injury and invading pathogens via rapid mobilization, engulfment, intracellular killing, and release of antimicrobial factors and neutrophil extracellular traps. However, a limited number of studies have addressed the physiological relevance of neuron-neutrophil interactions in host defense. Nevertheless, current knowledge points to an inhibitory role of the SNS on neutrophil activation. Noradrenaline was shown to suppress neutrophil chemotaxis, activation, and phagocytosis in stroke (152). Furthermore, it was recently reported that the sensory nervous system suppresses peripheral neutrophil–mediated immunity in the lung and skin (153, 154). Nociceptor TRPV1$^+$ sensory neurons release CGRP, suppressing pulmonary neutrophil recruitment and activation during *Staphylococcus aureus* lung infection (154) (**Figure 2*a***). Nevertheless, distinct sensory neuron subsets (TRPV1$^+$ and/or Nav1.8$^+$) may have different functional contributions in pulmonary immunity and barrier function. Nociceptor-derived CGRP was also shown to inhibit neutrophil recruitment and opsonophagocytic activity in the skin during *Streptococcus pyogenes* necrotizing infection (153). Bacteria directly activate TRPV1$^+$ nociceptor neurons through secretion of the pore-forming toxin streptolysin S, and nociceptor activation triggers local neuronal release of CGRP, mediating immune suppression (153). In both studies, a CGRP antagonist improved infection outcome (153, 154), suggesting that targeting this neuroimmune pathway could be a strategy to enhance host defense against invasive bacterial infections.

Neuron-mediated immune suppression during bacterial invasion can be detrimental. However, since pain accompanies inflammation, neuromodulation of neutrophils may provide a feedback mechanism to limit tissue damage by excessive inflammation (153). In addition, the impact of nociceptors in host defense may differ according to the type of pathogen. Neutrophil mobilization is protective in *S. aureus* pneumonia and *S. pyogenes* necrotizing fasciitis (153, 154). Thus, activation of immunosuppressive activity of nociceptors in these infections may mirror some degree of evolutionary pathogenic mechanisms. In contrast, sensory neurons promote host defense against skin infection with *Candida albicans* (155). Sensory neuron interactions with immune cells drive immune activation and inflammation in contact dermatitis (156, 157) and psoriasis (158) and mediate allergic airway inflammation in the respiratory tract (144, 159). Nevertheless, whether neuron-mediated immune suppression is context dependent and which signals might trigger a deleterious versus protective effect warrant clarification.

5.2. Neuron–Mast Cell Interactions

Close anatomical association between mast cells and sensory and autonomic neurons has been described at barrier sites, such as the skin and the respiratory and the intestinal mucosae. Thus, the existence of a bidirectional and functional neuron–mast cell axis has long been proposed. Several studies support that mast cell mediators, such as histamine, serotonin, and tryptase, induce nociceptor sensitization (160). Activation of nociceptors drives the release of neuropeptides, including CGRP, corticotropin-releasing hormone (CRH), VIP, and substance P (160). Neuropeptides

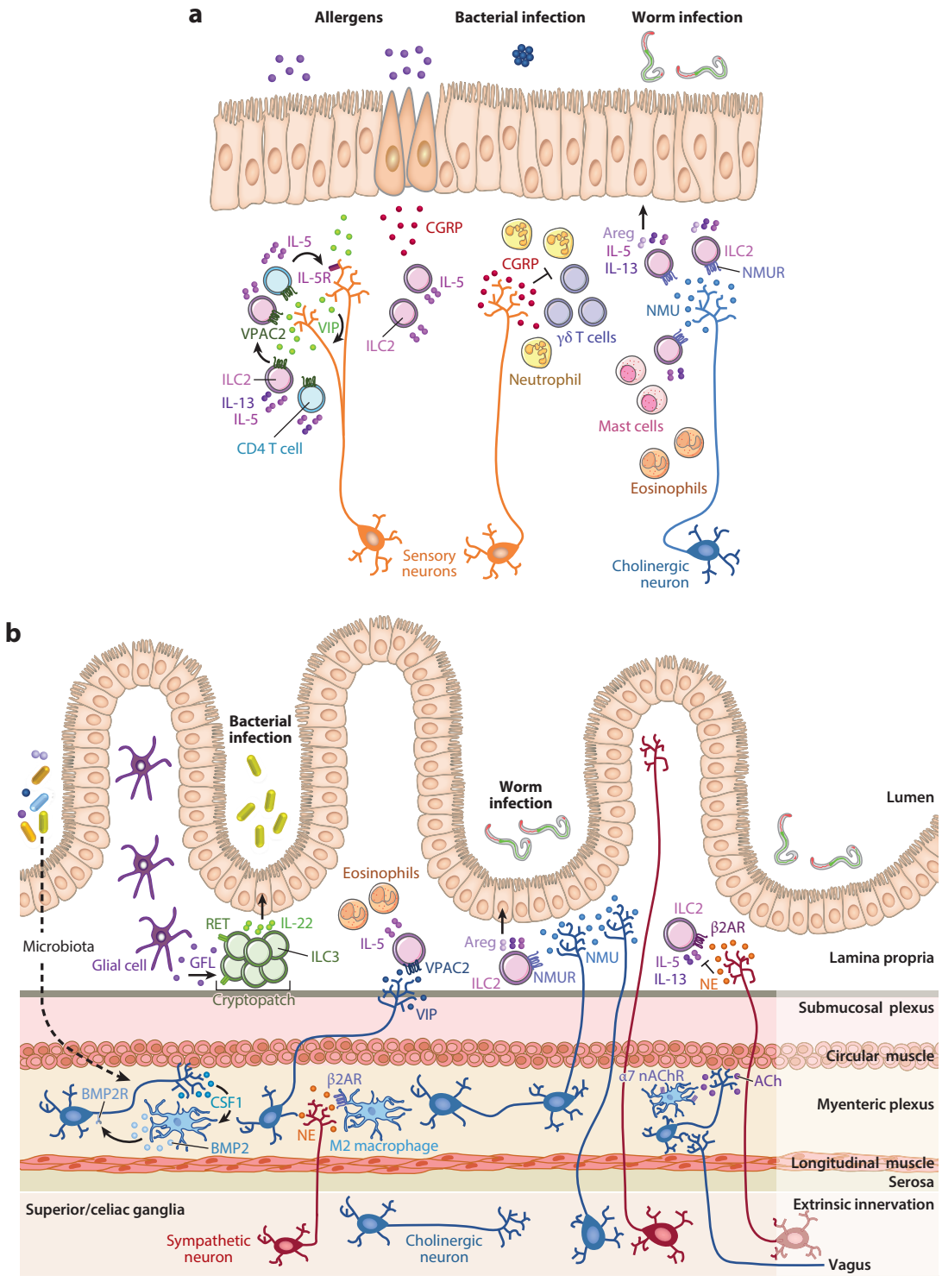

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Figure 2 (*Figure appears on preceding page*)

Neuro–immune cell units in the lung and intestine. (*a*) Pulmonary cholinergic neurons release NMU to stimulate ILC2s, promoting protective responses to parasites. Pulmonary sensory neurons also control ILC2 function through the release of CGRP, which stimulates IL-5 production. On the other hand, CGRP suppresses pulmonary neutrophil recruitment and activation, and resident γδ T cell–mediated host defense during *Staphylococcus aureus* lung infection. Sensory neuron–derived VIP increases IL-5 production by ILC2s, which stimulates nociceptors to produce increased VIP, generating a type 2 loop that potentiates allergy. (*b*) Enteric cholinergic neuron–derived NMU activates ILC2 responses and protects against helminth infection. Lamina propria ILC2 function is also regulated by VIP and NE. Glial cell–derived neurotrophic factors stimulate IL-22 production by lamina propria ILC3s, promoting barrier integrity. In the myenteric plexus, muscularis macrophages directly modulate neuronal function by secreting BMP2, which regulates peristaltic activity. SNS-derived NE induces a tissue-protective phenotype in muscularis macrophages. Cholinergic neuron–derived acetylcholine modulates macrophage activity reducing intestinal inflammation. Abbreviations: ACh, acetylcholine; α_7 nAChR, alpha 7 nicotinic acetylcholine receptor; Areg, amphiregulin; β2AR, β_2-adrenergic receptor; BMP2, bone morphogenetic protein 2; BMP2R, bone morphogenetic protein 2 receptor; CGRP, calcitonin gene–related peptide; CSF1, colony stimulating factor 1; NE, norepinephrine; NMU, neuromedin U; NMUR, neuromedin U receptor; SNS, sympathetic nervous system; VIP, vasoactive intestinal peptide; VPAC2, vasoactive intestinal peptide receptor 2.

stimulate mast cell activation and degranulation, thus creating a bidirectional positive-signaling loop that may result in neurogenic inflammation (160, 161). Stress can trigger the release of neuropeptides (substance P and CRH) that promote the release of mast cell mediators and increase mast cells' susceptibility to activation by bacterial antigens (160). Furthermore, neuron–mast cell interactions might have an important contribution to intestinal disorders, such as irritable bowel syndrome and inflammatory bowel disease (160, 162). Interactions between mast cells and sensory neurons have also been implicated in the pathophysiology of food and airway allergy and skin inflammation (163). Nevertheless, direct in vivo evidence of such neuroimmune functional units in the pathogenesis of allergic diseases is essentially lacking.

In addition to sensory neurons, sympathetic and cholinergic neurons might control mast cell function. Mast cells express β_2-adrenergic receptors, which upon activation inhibit the release of histamine and other inflammatory mediators (44). Evidence for parasympathetic regulation of mast cells comes from several findings: (*a*) Intestinal mucosal mast cells contact vagal afferent terminals; (*b*) nAChRs and muscarinic cholinergic receptors are expressed by mast cells; (*c*) vagal stimulation or acetylcholine administration increases histamine in intestinal mast cells; and (*d*) nAChR agonists attenuate mast cell responses (164).

5.3. Neuron-Macrophage Interactions

Tissue-resident macrophages are highly heterogeneous and specialized phagocytes found in most body tissues. Macrophages recognize, engulf, and destroy target cells, present antigens to T cells, and initiate inflammatory processes. Macrophage-induced inflammatory effects are well known to be counteracted by the autonomic nervous system (53). Accordingly, the involvement of macrophages in the cholinergic anti-inflammatory pathway has been an area of extensive research (53, 165–167). Herein, we highlight recent studies that have been identifying macrophages as part of functional NICUs that regulate tissue-specific processes in the intestine and adipose tissue.

In the intestine, neuron-macrophage interactions regulate intestinal motility (127) and promote tissue protection during injury and infection (78, 168) (**Figure 2*b***). In a mouse model of postoperative ileus, in which inflammation of the muscle layer impairs the contractility of the intestine, stimulation of the vagus nerve reduced intestinal inflammation and improved disease outcome (78). This process requires α_7 nAChR expression on muscularis macrophages. Vagus nerve endings synapse with cholinergic myenteric neurons, in close contact with muscularis macrophages expressing α_7 nAChR. Therefore, it has been proposed that vagal signals, through the ENS, modulate intestinal macrophage responses, inflammation, and, consequently, gut function (78).

The relevance of the neuron-macrophage cross talk is further supported by studies showing that, in steady state, enteric neurons maintain muscularis macrophages through secretion of CSF1, a growth factor required for macrophage development (127). Reciprocally, muscularis macrophages can directly modulate neuronal function by secreting BMP2, which activates BMP receptor (BMPR)-expressing enteric neurons (127). This bidirectional cross talk regulates the peristaltic activity of the colon. Interestingly, commensal microbe-derived signals modulated BMP2 and CSF1 expression by macrophages and enteric neurons, respectively (127). This suggests that an intricate microbe-neuron-macrophage axis controls gastrointestinal motility, contributing to tissue homeostasis in steady-state conditions (127).

Using imaging and transcriptional profiling tools, Gabanyi and colleagues (168) demonstrated that intestinal macrophages exhibit intratissue specialization and compartmentalization. Lamina propria macrophages are similar to M1 (proinflammatory) macrophages, whereas muscularis macrophages display a tissue-protective program, being phenotypically similar to M2 (regulatory) macrophages. Activation of extrinsic sympathetic ganglia by enteric bacterial infection further enhances the tissue-protective profile of muscularis macrophages, via norepinephrine signaling in β_2-adrenergic receptor–expressing macrophages (168).

Maintenance of an anti-inflammatory tissue environment is vital to preserve intestinal tissue homeostasis. Moreover, this is of special relevance in tissues where cells with reduced proliferative or regenerative potential are present, such as neurons. Therefore, striking parallels can be made between the gut and the CNS, where neuronal signals maintain the anti-inflammatory state of microglia, the CNS-resident macrophages (169). While these studies clearly demonstrate the relevance of neuron-macrophage cross talk for intestinal physiology, the neuronal sensing mechanisms by which luminal aggressions are detected, the potential involvement of both extrinsic and intrinsic innervation, and the exact circuits (afferent and efferent) involved in this process remain unknown. How dysregulated interactions between neurons and macrophages might contribute to tissue damage in gastrointestinal disorders and which signals might trigger such conditions also deserve attention.

Akin to their intestinal counterparts, specialized macrophages in the adipose tissue were recently shown to respond to neuronal cues (170) (**Figure 3*a***). Pirzgalska and colleagues (170) identified a discrete population of macrophages tightly associated with sympathetic axons innervating the white adipose tissue, which the authors named sympathetic neuron–associated macrophages (SAMs). Importantly, SAMs take up and catabolize norepinephrine through expression of the norepinephrine transporter SLC6A2 and the norepinephrine-degrading enzyme monoamine oxidase A, respectively. Activation of the SNS, through optogenetics, resulted in increased norepinephrine uptake by SAMs. Additionally, genetic ablation of *Slc6a2* in hematopoietic cells improved browning of white adipose tissue, increased thermogenesis and fat oxidation, and resulted in sustained weight loss in obese mice (170). A similar macrophage-mediated norepinephrine-degrading activity that compromises lipolysis was reported in the adipose tissue during aging (171). Nevertheless, whether the decline of lipolysis with aging is associated with increased SAMs in adipose tissue remains unclear. Tissue-resident macrophages were also found to control sympathetic innervation of brown adipose tissue, thus indirectly controlling local norepinephrine signaling, thermogenesis, and obesity (172). Hence, similarly to microglia in the brain and muscularis macrophages in the small intestine, adipose tissue macrophages seem to function as important hubs that integrate neuron-derived cues. Thus, it is tempting to speculate that brain, small intestine, and adipose tissue (and perhaps other tissues) have parallel mechanisms of macrophage-mediated neuronal protection in steady-state conditions and that disrupting the macrophage-neuron axis might result in tissue-specific pathology.

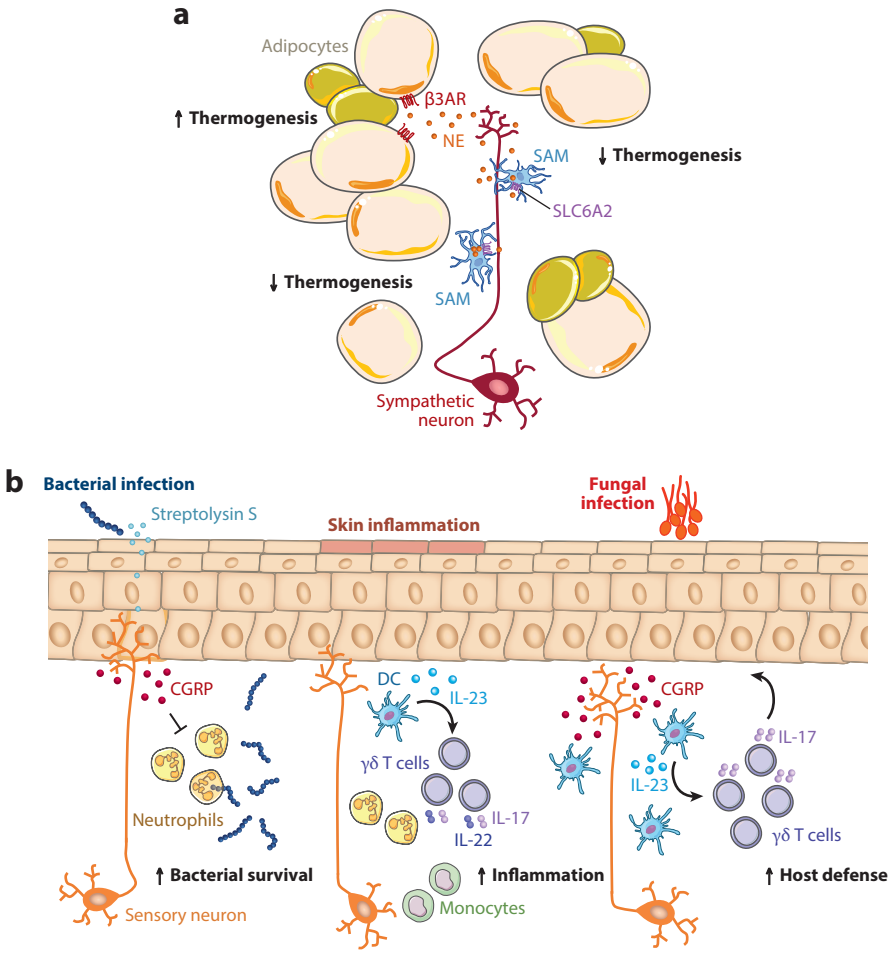

Figure 3

Neuro–immune cell units in adipose tissue and skin. (*a*) NE released by sympathetic neurons in the adipose tissue can be scavenged by SAMs through the NE transporter SLC6A2, possibly to prevent tissue-damaging NE spillover. Scavenging of NE also prevents the activation of the thermogenesis process via β3AR activation in adipocytes. (*b*) Sensory neurons in the skin are activated by *Streptococcus pyogenes*–derived streptolysin S toxin and release CGRP, mediating suppression of peripheral neutrophil–mediated immunity. DCs can also be modulated by sensory-derived CGRP in skin inflammation and *Candida albicans* infection. $Na_V1.8^+$ $TRPV1^+$ nociceptor neurons induce IL-23 production by nearby dermal DCs, which then act on $IL\text{-}23R^+$ γδ T cells to produce IL-17 and IL-22. Abbreviations: β3AR, β_3-adrenergic receptor; CGRP, calcitonin gene–related peptide; DC, dendritic cell; NE, norepinephrine; SAM, sympathetic neuron–associated macrophage; SLC6A2, solute carrier family 6 member 2; TRPV1, transient receptor potential cation channel subfamily V member 1.

5.4. Neuron–Innate Lymphoid Cell Units

In the last decade, innate lymphoid cells (ILCs) have emerged as critical integrators of complex environmental and host-derived cues, playing key roles in lymphoid organogenesis, immunity to infection, inflammation, tissue remodeling, metabolic homeostasis, and cancer (173). At mucosal

barriers ILCs reside in close proximity to neurons and glial cells, and multiple studies have explored the physiological relevance of such functional neuron-ILC units (174) (**Figure 2**).

In the lung and small intestine, group 2 ILCs (ILC2s) respond to VIP through VPAC2 receptor–mediated signaling, which results in increased IL-5 production (144, 175). Innate IL-5 and IL-13 coexpression is enhanced after caloric intake, linking eosinophil levels with metabolic cycling (175). In the lung, VIP released by nodose afferent nociceptor sensory neurons stimulates ILC2s to produce IL-5, which can act directly on nociceptors, further increasing VIP expression and generating a type 2 inflammatory signaling loop that potentiates allergic inflammation (144). Strikingly, pulmonary neuroendocrine cells (PNECs), a rare population of airway epithelial cells that secrete GABA under the control of a neural circuitry (176), were also found to be in close proximity with ILC2s and to potentiate allergic asthma responses (177). Upon allergen challenge, PNECs enhance ILC2 cytokine production through CGRP secretion (177). Three other independent studies provided additional insight into how neuron-ILC2 interactions regulate type 2 immune responses. In response to helminthic infection or allergens, pulmonary and intestinal cholinergic neurons regulate ILC2 function via production of neuromedin U (NMU) (178–180). NMU signals through NMU receptor 1 (NMUR1) expressed in ILC2s and leads to a rapid and potent production of type 2 inflammatory cytokines, IL-5 and IL-13, and of the tissue-protective cytokine amphiregulin (178, 180). In vivo activation of this signaling axis enhances ILC2 responses and confers immediate tissue protection to helminthic infection. Subsequently, neuron-ILC2 units were identified as part of a neuron-based regulatory circuit that dampens ILC2-mediated type 2 inflammation (181). ILC2s express the β_2-adrenergic receptor and colocalize with adrenergic neurons in the intestine. Abrogation of β_2-adrenergic receptor–mediated signaling resulted in increased ILC2 responses, type 2 inflammation, and lower helminth infection burden, effects that were reversed by β_2-adrenergic receptor agonist treatment (181). Together, these studies demonstrate that ILC2s can integrate distinct neuronal pathways—the cholinergic and sympathetic—revealing complex regulatory mechanisms by which ILC2 responses can be turned on and off. Thus, one can speculate that neuron-ILC2 units might regulate the balance between protective and pathological type 2 immune responses in health and disease.

A pioneering study revealed that enteric ILC3s are part of neuroglia-ILC3 units orchestrated by neurotrophic factors (92). Enteric glial cells sense microbial and host alarmin cues, which leads to increased glia-derived production of neurotrophic factors that in turn induce IL-22 production by RET-expressing ILC3s. Consequently, this glia-ILC3 axis is necessary for intestinal tissue repair upon inflammatory and infection insults (92). In addition to local neural cues, vagus nerve–derived signals have also been implicated in the regulation of ILC3 responses to bacterial infections in the peritoneal cavity (182). Importantly, glial cells and mucosal neurons were shown to sense local environmental perturbations, notably microbial cues, worm products, and host alarmins, through MYD88-dependent signaling (92, 178). Enteric neural cells can therefore coordinate ILC-mediated immune responses through the production of ILC-activating neuroregulators (92, 178). These seminal studies uncovering how neuron-ILC units trigger fast tissue protection through coordinated neuroimmune responses hold promise for targeting NICUs to fine-tune immune responses by dampening excessive detrimental inflammation or potentiating protective immunity and tissue repair.

Natural killer (NK) cells were identified in the early 1970s due to their ability to spontaneously kill leukemia cells and are now known as key effectors in cancer immunosurveillance, viral immunity, transplantation rejection, and autoimmunity (183). Nevertheless, whether NK cells establish functional interactions with neurons is mostly unexplored. Early studies indicate that catecholamines can have a dual time-dependent effect on NK cells. Catecholamines were

shown to increase circulating NK cell numbers in an acute manner (184), whereas chronic stress or prolonged in vivo treatment with β_2-adrenergic receptor agonists suppresses circulating NK cell numbers and activity (185). α_1- and α_2-adrenergic receptor mRNAs have also been detected in splenic NK cells, and agonist activation of either subtype increases NK cell cytotoxicity (186). More recently, reciprocal interactions between neural stem cells and NK cells in the brain were found to regulate neuroregenerative processes during neurological inflammatory disorders (187). During the chronic phase of multiple sclerosis in humans and experimental autoimmune encephalomyelitis (EAE) in mice, NK cells are retained in the subventricular zone of the brain, where they preferentially localize nearby neural stem cells. Neural stem cell–derived IL-15 sustains NK cell proliferation, survival, and function (187). In turn, NK cells inhibit neural stem cells, impairing their neuronal repair capacity, and NK cell removal promotes EAE recovery. Thus, neural stem cell–NK cell units in the brain regulate tissue repair and recovery from inflammation.

5.5. Neuron-DC Interactions

DCs are professional antigen-presenting cells with key roles in the initiation and regulation of adaptive immune responses. DCs recognize, process, and present antigens to T cells and, depending on the context of antigen presentation, can either promote T cell activation and differentiation or induce tolerance and differentiation of Tregs (188). Expression of adrenergic and neuropeptide receptors by DCs suggests that neuronal cues may modulate DC function. Therefore, several studies have addressed the impact of catecholamines and neuropeptides on DCs, while less attention has been given to cholinergic effects (189, 190). β_2-adrenergic receptor signaling in DCs was shown to inhibit antigen cross-presentation to CD8 T cells, to suppress Th1 immune responses, and to promote Th2 and Th17 responses (44, 189). In contrast, stimulation of α-adrenergic receptors enhances antigen uptake and endocytosis and modulates DC migration (44, 189). VIP was also shown to regulate DCs, notably by inducing regulatory and tolerogenic DCs, which promote differentiation of Tregs, with important implications in autoimmune disorders and in transplantation (191–193). However, most of these studies were based on in vitro observations or in vivo administration of catecholamines or neuropeptides. Thus, evidence for cell-intrinsic neuron-DC interactions in vivo is still missing. Nevertheless, two recent studies described neuron-DC cross talk taking place in the skin (155, 158). Skin nociceptor neurons interact with DCs and modulate the IL-23/IL-17 pathway in the context of infection and inflammation (155, 158) (**Figure 3*b***). $Na_v1.8^+$ $TRPV1^+$ nociceptor neurons induce IL-23 production by nearby dermal DCs, which then act on $IL\text{-}23R^+$ $\gamma\delta$ T cells to produce IL-17F and IL-22. This results in recruitment of circulating neutrophils and monocytes, driving skin inflammation (158). In a subsequent study, sensory neurons were found to sense *Candida albicans* and enhance host resistance via secretion of the neuropeptide CGRP. CGRP triggered IL-23 production from DCs that then elicited protective IL-17A production from dermal $\gamma\delta$ T cells, consequently controlling infection (155). Thus, these studies indicate that nociceptor fibers can integrate environmental signals to modulate local DC-mediated innate immune responses to infection and inflammation. Nevertheless, whether peripheral neurons can interact and directly modulate the activity of $\gamma\delta$ T cells and how neuron-DC interactions modulate adaptive T cell responses in vivo are currently unknown.

5.6. Neuron–T Cell Interactions

Autonomic regulation of adaptive immunity has long been appreciated, with most studies focusing on the impact of catecholamines in T and B lymphocyte function. The prevailing perspective is

that the SNS modulates T and B lymphocytes, via β_2-adrenergic receptor signaling, suppressing Th1 and promoting Th2, Th17, Treg, and antibody responses (44, 194). However, most of these studies were based on in vitro or ex vivo approaches following administration of adrenergic agonists/antagonists, or in vivo strategies to manipulate sympathetic neurotransmission. Thus, evidence for cell-intrinsic neuron-lymphocyte interactions in vivo is still missing.

In addition to the potential modulation of lymphocyte functions, adrenergic signals were also shown to control lymphocyte trafficking (195), and T cell–intrinsic circadian clocks imprint rhythmicity to lymphocyte migration (196). Thus, akin to HSCs, lymphocyte behavior might be modulated by the molecular clock via adrenergic signals. Nevertheless, whether the circadian neuronal axis is operational in T lymphocytes is currently unknown.

Reciprocally, lymphocytes can modulate neuronal signals, as illustrated by the cholinergic anti-inflammatory pathway. Vagus nerve stimulation requires sympathetic β_2-adrenergic receptor signaling on CD4 lymphocytes to induce T cell–derived acetylcholine. The resulting CD4 T cell–derived acetylcholine activates nAChR expressed by splenic macrophages, suppressing the production of TNF-α and other proinflammatory cytokines (52, 54). Thus, in addition to local modulation of inflammation, neuron-lymphocyte interactions can also play a role in complex neuroimmunomodulatory circuits (4). Finally, the impact of lymphocytes on CNS neurons, neurophysiology, and behavior is an area of extensive research in the neuroimmunology field (197). Several lymphocyte-CNS interactions have been documented in health and disease (197); some of these aspects are discussed in Section 4.

6. CONCLUDING REMARKS AND PERSPECTIVES

Known parallels between the immune and nervous systems suggest that intricate interactions between these systems might jointly integrate environmental cues and coordinate physiological processes (2, 5). While the role of inflammation in neuronal function and the impact of neuron-derived molecules in immune cells have been explored in the last decades, the more recent elucidation of NICUs as critical regulators of tissue homeostasis and physiology has revealed a picture that is far more complex than initially predicted (1). The complexity of NICUs is reflected in the myriad of tissues where they are present, the diversity of neurons and immune cell types they combine, the neuronal circuits they integrate, and the range of physiological processes they modulate. NICUs sense and integrate multiple environmental and host-derived signals and coordinate neuroimmune communication pathways to orchestrate tissue homeostasis. Thus, these coordinated neuroimmune regulatory responses might have been evolutionarily preserved to ensure organismal homeostasis throughout evolution.

The remarkable recent progress on the understanding of neuroimmune interactions is raising even more complex and exciting questions that warrant implementation of novel interdisciplinary approaches. Future challenges include the definition of local, regional, and systemic neuronal and immune circuits that communicate with discrete NICUs. State-of-the-art tools developed to target neuronal activity in vivo, such as optogenetics and chemogenetics, might help in deciphering some of these aspects.

Another remarkable challenge concerns the exploration of the potential of NICUs as therapy targets. Insights into the molecular mechanisms involved in neuroimmune interactions have been explored as new therapeutic possibilities in the clinical settings of inflammatory and autoimmune diseases. The main neuroimmune pathways that were therapeutically explored comprise the modulation of the inflammatory reflex through electrical vagus nerve stimulation. Pharmacological approaches, including α_7 nAChR agonists, acetylcholinesterase inhibitors, muscarinic acetylcholine receptor agonists, and β_2-adrenoreceptor agonists, are also being explored

(198–208). Galantamine, an acetylcholinesterase inhibitor acting on the CNS, and in clinical use to treat Alzheimer disease, is currently being tested in a clinical trial, as a pharmacological approach for neuronal modulation of inflammation, in patients with metabolic syndrome (200, 207, 209). In addition to pharmacological therapies, electroacupuncture and implantable bioelectronic devices are being successfully explored as treatment strategies in which neural circuits are modulated to deliver anti-inflammatory signals to target organs. Electroacupuncture is able to trigger brain AChR-mediated signaling, which results in catecholaminergic signaling in the spleen through efferent vagus nerve activity. The result of this vagal stimulation is a reduction in proinflammatory cytokines that improves survival in an endotoxemia model (210). Similarly, electric stimulation of the sciatic nerve increases dopamine secretion in the adrenal medulla, suppressing the systemic inflammatory response, which results in increased survival in murine sepsis (211). Electric modulation of the inflammatory reflex has also been explored in the clinical context, in rheumatoid arthritis and inflammatory bowel disease conditions (212, 213). A recent clinical trial using a bioelectronic device for vagal stimulation demonstrated potential in reducing disease severity in 17 rheumatoid arthritis patients (212). In Crohn disease, vagal stimulation may also be a valuable therapeutic tool, since current pharmacological approaches have side effects and clinical studies have established that vagus nerve tone is attenuated in patients with this condition. This potential was demonstrated in a small clinical trial in which electrical vagus nerve stimulation was performed in 7 Crohn disease patients, resulting in disease remission at six months (213). The positive results of vagal stimulation in the clinical setting show promise for the establishment of bioelectronic devices as an alternative to pharmacological approaches. Therefore, a detailed understanding of the specificity of the molecular fingerprints and cellular players involved in NICUs holds promise for the discovery of novel therapeutic targets and the implementation of innovative therapies in the context of inflammatory, infectious, metabolic, and oncogenic conditions that are important public health concerns.

Still, many other aspects remain unexplored: Are NICUs regulated by the CNS? And conversely, can peripheral information from NICUs reach the brain and affect neuronal processes and behavior? Addressing the molecular, cellular, and circuitry aspects of bidirectional neuroimmune interactions is a major challenge for the decades to come. Nevertheless, it is tempting to speculate that peripheral NICUs might allow for sensing of environmental and endogenous threats, jointly hardwiring the CNS and peripheral organs, to maintain organismal homeostasis in health and disease.

FUTURE ISSUES

1. Uncover novel multiple-tissue NICUs and their impact on tissue physiology.
2. Address the spatiotemporal dynamics of NICUs.
3. Explore the potential of NICUs for therapy targeting and design.
4. Map local and regional neuronal and immune circuits connecting to NICUs.
5. Explore the role of NICUs in hardwiring the CNS.
6. Explore the role of NICUs in organismal homeostasis in health and disease.

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