Immunity

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Review

Sensory neurons: An integrated component of innate immunity

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SUMMARY

The sensory nervous system possesses the ability to integrate exogenous threats and endogenous signals to mediate downstream effector functions. Sensory neurons have been shown to activate or suppress host defense and immunity against pathogens, depending on the tissue and disease state. Through this lens, pro- and anti-inflammatory neuroimmune effector functions can be interpreted as evolutionary adaptations by host or pathogen. Here, we discuss recent and impactful examples of neuroimmune circuitry that regulate tissue homeostasis, autoinflammation, and host defense. Apparently paradoxical or conflicting reports in the literature also highlight the complexity of neuroimmune interactions that may depend on tissue- and microbe-specific cues. These findings expand our understanding of the nuanced mechanisms and the greater context of sensory neurons in innate immunity.

INTRODUCTION

The ability to sense and respond to danger is critical for the maintenance of health and tissue protection, and multicellular organisms have evolved several systems to perform these functions. Like the innate immune system, the peripheral nervous system is equipped with molecular sensors that specifically detect signals of infection or tissue damage and can elaborate soluble effector factors that coordinate host responses (Figure 1A). Barrier tissues are the body's first line of defense against invading pathogens and environmental insults. Clinical observations have long hinted at a link between the peripheral nervous system and tissue inflammation. For example, some patients who experience injuries resulting in focal denervation report significant improvement in inflammatory conditions in those tissue sites, and there are also cases of patients with nerve damage who experience increased susceptibility to bacterial infections.[1–4] Additionally, nerve stimulation therapy has been found to alleviate symptoms of autoimmune conditions.[5,6] Recent advances in neuroimmunology have revealed mechanisms by which sensory neurons function as innate immune sensors and effectors. This review will focus on the role of sensory and, to a lesser extent, autonomic neurons in maintaining tissue homeostasis and mediating innate immunity because these neuronal subtypes are well-equipped to perform those functions. Specifically, we will highlight some of the most important and compelling studies showing how sensory neurons regulate tissue homeostasis and host defense. Because of the rapid growth of the field and abundance of articles on this topic, this review is not exhaustive but instead aims to spotlight some of the most exciting pathways discovered so far.

Sensory neurons form the afferent branch of the peripheral nervous system, extending dendrites into barrier tissue sites like the skin, lung, and gut. Autonomic afferent neurons receive input from visceral organs. Signals from peripheral or visceral organs are received by peripheral nerve terminals and transmitted to neuron cell bodies before finally reaching the central nervous system (CNS). Depending on which organ they innervate, sensory neuron cell bodies are found in dorsal root ganglia (DRG) that are close to the spinal cord, trigeminal ganglia (TG) in the cranium, jugular and nodose ganglia in the neck, or myenteric and submucosal plexus layers of the gut (Figure 1B). Specialized subtypes of sensory neurons, such as proprioceptors, mechanoreceptors, thermoreceptors, and nociceptors (pain-mediating neurons), are tuned to detect specific stimuli. Their neuronal dendrites express receptors for various sensory stimuli, including noxious/harmful substances, as well as ion channels that rapidly transduce extracellular signals into intracellular calcium influx and action potentials. Nociceptors detect stimuli such as mechanical force, harmful temperatures or chemicals, injury-related signals, and microbial components. Nociceptors can be divided into two major classes: those that possess medium-diameter, thinly myelinated axons (Aδ-fibers) with small receptive fields and those with small-diameter unmyelinated axons (C-fibers) with large receptive fields. Within these two categories, Aδ neurons can be further divided into type I (high threshold mechanical) nociceptors that respond to mechanical and chemical stimuli and type II (mechanically insensitive) nociceptors that have a much lower heat threshold. Most C-fibers are polymodal and can be classified into peptidergic (containing the neuropeptides Substance P (SP) or calcitonin gene-related peptide [CGRP]) or non-peptidergic (not expressing SP or CGRP) (Table 1).[7,8]

Painful or itchy (pruritogenic) stimuli are detected by distinct neuron receptors. TRPV1 and TRPA1 are members of the Transient Receptor Potential (TRP) family of ligand-gated cation

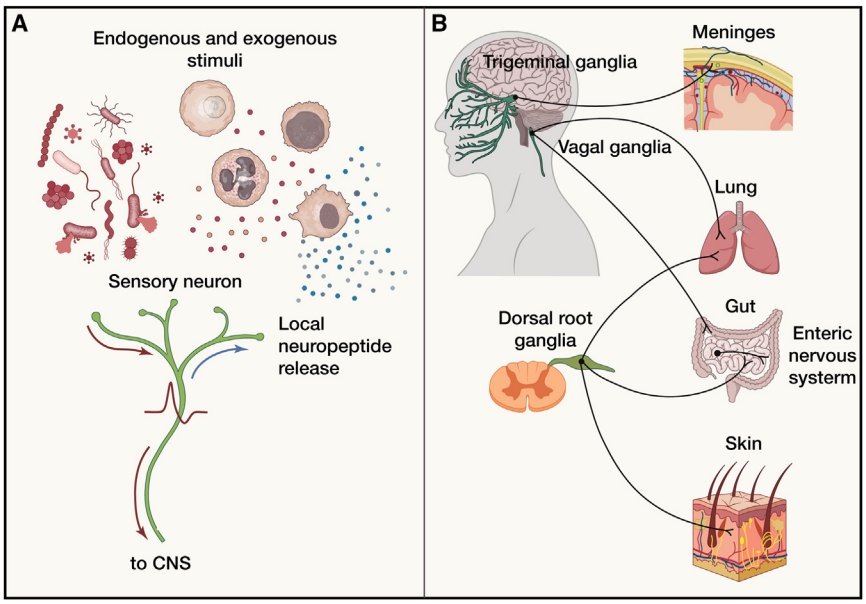

Figure 1. Sensory neurons participate in innate immunity

(A) Neurons can detect endogenous and exogenous signals of infection, inflammation, and tissue damage and release neuropeptides and neurotransmitters to regulate immune responses.

(B) Sensory neuron cell bodies reside in ganglia, and their peripheral nerve terminals innervate barrier tissues.

channels. These ion channels detect noxious heat, capsaicin, mustard oil, reactive electrophiles, and other potentially harmful stimuli.[9] Their activation leads to pain sensation and mediates neurogenic inflammation. NAV1.8 is a voltage-gated sodium channel that is highly and selectively expressed by sensory neurons.[10] Non-peptidergic neurons are linked to itch sensation and express pruritogen receptors such as histamine receptors, members of the Mas-related family of G-protein-coupled receptors (MRGPRs), and proteinase-activated receptors (PARs).[11] Non-peptidergic neurons expressing a $G\alpha_i$-interacting protein (GINIP) also participate in peripheral inflammation and pain sensation by releasing immune-regulating neuropeptides into innervated tissues and mediating presynaptic inhibitory pathways of analgesia.[12,13]

Sensory neurons directly participate in local immunity. Upon activation, sensory neurons relay this signal to the CNS to be perceived as pain or itch. Simultaneously, antidromically conducted action potentials travel toward peripheral nerve terminals. In this axon reflex,[14] neuropeptides and neurotransmitters are rapidly released from nerve terminals to act directly on neighboring immune and non-immune cells. Here, we will discuss some of the most compelling and interesting pathways by which neurons sense exogenous and endogenous signals and effect tissue homeostasis, autoinflammation, and innate immunity to infectious pathogens. This review article will focus on the effector functions of neuropeptides SP, CGRP, neuromedin U (NMU), vasoactive intestinal peptide (VIP), and TAFA chemokine like family member 4 (TAFA4) as well as the neurotransmitters acetylcholine (Ach) and glutamate (Table 2).

The release of neuropeptides and neurotransmitters into peripheral tissues is one of the most well-studied mechanisms by which tissue-innervating neurons communicate with local immune and non-immune cells. SP, encoded by *Tac1*, is a small neuropeptide composed of 11 amino acids (aa) that can signal through multiple unique G-protein-coupled receptors (GPCRs) including MRGPR member A1 (MRGPRA1), MRGPR B2 (MRGPRB2), and Neurokinin-1 receptor (NK1R), which will be highlighted in this review.[3,15–19] CGRP, a 37 aa neuropeptide, exists in two isoforms, CGRPα (produced via alternative splicing of the calcitonin-coding *Calca* transcript) and CGRPβ (encoded by the separate *Calcb* gene).[20,21] Both isoforms signal through the heterodimeric CGRP-specific receptor formed by calcitonin-receptor-like receptor (CALCRL) and receptor activity-modifying protein 1 (RAMP1). While RAMP1 determines the specificity of this receptor, CALCRL is a GPCR that interacts with an accessory protein called receptor component protein (RCP) and a $G\alpha_s$ subunit to transduce CGRP signaling to the intracellular cyclic AMP (cAMP)-mediated transcriptional changes.[22,23] NMU is observed in two forms, a full-length 17–40 aa polypeptide or a truncated 8–9 aa polypeptide, both of which are conserved throughout evolution and are functionally active.[24–27] NMU can signal through separate GPCRs, namely, neuromedin U receptor 1 (NMUR1) and neuromedin U receptor 2 (NMUR2), with the first being enriched in peripheral tissues and the second primarily observed in the CNS.[28] As a neuropeptide effector, NMU signaling through NMUR1 drives $G\alpha_q$-mediated calcium flux and downstream transcription factor activation.[29] VIP is a 28 aa polypeptide that is broadly expressed throughout the body and released at nerve endings, and it can be produced by immune cells.[30–34] VIP can also act on immune cells via three broadly expressed GPCRs, VIP receptor type 1 (VPAC1), VIP receptor type 2 (VPAC2), and pituitary adenylyl cyclase-active peptide type 1 receptor (PAC1), all of which can couple to $G\alpha_s$ and induce cAMP accumulation and protein kinase A (PKA) activity.[35–38] PAC1 activation can also signal via $G\alpha_q$-mediated calcium flux and protein kinase C (PKC) activation.[39] TAFA4 (aka FAM19A4), encoded by *Tafa4* and member of the chemokine like TAFA family, is a 95 aa secreted polypeptide primarily expressed by neuronal tissues.[40] TAFA4 is an endogenous ligand of formyl peptide receptor 1 (FPR1), a G-protein-coupled formylated peptide receptor implicated in chemotaxis and activation of innate effectors.[41] However, TAFA4 likely acts on other receptors that are yet to be defined.[13,42] Ach is a small, fast-acting neurotransmitter simply composed of an acetyl group and a cationic choline group. Ach is broadly expressed throughout the nervous system and mediates neuron-neuron communication as well as communication between the CNS and peripheral tissues.[43–46] Ach can signal via two classes of receptors, nicotinic and muscarinic Ach receptors (nAchR and mAchR, respectively), which have diverse and cell-specific expression patterns throughout the nervous

Table 1. Sensory neuron markers, characteristics, and functions in regulating immunity

Category	Markers	Characteristics	Location of cell body	Location of nerve terminal	Type of immunity regulated
Peptidergic nociceptors	• CGRP • SP • NAV1.8 • TRPV1 • TRPA1	thinly myelinated Aδ or unmyelinated C-fibers	DRG VG TG	skin, lung, and gut lung and gut meninges	• tissue homeostasis • radiation-induced skin inflammation • skin autoinflammation • lung and gut allergic inflammation • defense against pathogens
Non-peptidergic nociceptors and pruriceptors	• NAV1.8 • MRGPRD TRPA1(NP1) • MRGPRA3 CGRP (NP2) • NPPB TRPV1 (NP3)	unmyelinated C-fibers	DRG	skin	• autoinflammation • type-2 inflammation
Enteric sensory neurons	• NMU • CGRP	multipolar neurons	gut	gut	• type-2 inflammation

system, innervated tissues, and immune system.[47,48] Glutamate, a free α amino acid, is a major excitatory neurotransmitter in the CNS and is stored in abundance in synaptic vesicles, permitting rapid exocytosis.[49] Glutamate can signal through many different receptors that are categorized as either ionotropic glutamate receptors (iGluRs), which are ligand-gated ion channels, or metabotropic glutamate receptors (mGluRs), which are GPCRs.[50] All these neurotransmitters and neuropeptides are beginning to gain attention for their participation in immune pathways in peripheral tissues.

NEUROIMMUNE AND NEUROEPITHELIAL CROSSTALK REGULATES BARRIER TISSUE HOMEOSTASIS

Sensory neurons in the gut play important roles in maintaining the epithelial barrier and regulating the microbiome (Figure 2A). For example, using a NAV1.8-Cre reporter to broadly label gut-innervating nociceptors, it was found that NAV1.8$^+$ neurons exist in close proximity to mucus-secreting goblet cells.[51] Interestingly, ablation of NAV1.8$^+$ neurons resulted in significantly reduced mucus thickness, while use of a DREADD (designer receptor exclusively activated by designer drugs) system to selectively activate NAV1.8$^+$ neurons was sufficient to induce mucus production by neighboring goblet cells. Mechanistically, the authors found that NAV1.8$^+$ neurons mediated mucus production by releasing CGRP, which signaled through RAMP1 on goblet cells. Remarkably, the steady-state production of CGRP in the gut was attenuated in germ-free (GF) mice compared with specific-pathogen-free (SPF) counterparts. The authors also found that fecal microbiota transfer (FMT) from SPF mice to GF recipients was sufficient to induce the production of neuronal CGRP in the gut, suggesting that the gut microbiome mediates neuro-epithelial crosstalk and mucus secretion. Ablation of NAV1.8$^+$ neurons also conferred intestinal flora dysbiosis and an augmented endoplasmic reticulum (ER) stress signature in gut epithelial cells at steady state, as well as exacerbated disease in a dextran sulfate sodium (DSS)-induced model of colitis. Together, these findings illustrate a pathway in which the gut microbiome acts through sensory neurons to drive the production of CGRP and maintain steady-state mucus production, microbial diversity, and immune homeostasis.[51]

In complementary work, DREADD-mediated silencing or chemical ablation of TRPV1$^+$ neurons both promoted microbial dysbiosis and exacerbated disease severity in DSS colitis.[52] Notably, both dysbiosis and increased disease severity were transmissible to GF mice following FMT from TRPV1$^+$-neuron-ablated mice. In these studies, global ablation of the SP-coding gene *Tac1* recapitulated disease severity and dysbiosis observed in TRPV1$^+$-neuron-ablated mice, implicating this neuropeptide as an important mediator of gut flora homeostasis and epithelial barrier protection. Potentially, the most remarkable finding among these studies was that the exacerbated DSS disease phenotype in *Tac1*-ablated mice was entirely abolished when these mice were cohoused with *Tac1*-sufficient mice. Together, these data suggest that TRPV1$^+$ neurons regulate the gut flora and maintain immune homeostasis through SP. Although the mechanisms of gut flora homeostasis differ, both studies described a common microbial dysbiosis that enriched for *Firmicutes* families (*Turibacteriaceae* and *Erysipelotrichaceae*), which have been implicated as potential mediators of gut inflammation.[51–55] The clinical significance of this pathway is supported by the observation that TRPV1$^+$ innervation is attenuated in the intestines of patients with inflammatory bowel disease (IBD).[52]

In another example of neuronal contribution to gut homeostasis, TRPV1$^+$ neurons were shown to limit small intestine invasion by the enteric pathogen *Salmonella enterica* serovar Typhimurium (STm) in mice.[56] During infection, STm penetrate the gut epithelium by passing through microfold cells (M cells). Mice deficient in TRPV1$^+$ neurons or CGRP exhibited increased abundance of M cells and a reduction in protective segmented filamentous bacteria (SFB) in the ileum of naive and STm-infected mice[56] (Figure 2A). These phenotypic changes translated to increased STm burden during infection. Mechanistically, the authors found that TRPV1$^+$ neurons secreted CGRP, which modulated the frequency of M cells found within Peyer's patches and promoted colonization by SFB that protect against *Salmonella* infection. Together, these reports identify multiple mechanisms by which neural crosstalk with the gut epithelium (M cells, goblet

Table 2. Summary of sensory neuropeptide and neurotransmitter roles in innate immunity

Neuropeptide/ neurotransmitter	Gene	Source neurons	Receptors	Immune/effector cell expression of receptors	Effector functions
Substance P	*Tac1*	• TRPV1$^+$ neurons	• MRGPRA1 • MRGPRB2 • NK1R	• dDC2s (MRGPRA1) • mast cells (MRGPRB2)	• increase mast cell degranulation and skin inflammation • induce dDC2 migration and Th2 immunity • regulate intestinal inflammation and defense against *C. difficile*
CGRPα/CGRPβ	*Calca*, *Calcb*	• NAV1.8$^+$ neurons • TRPV1$^+$ neurons • ChAT$^+$ enteric neurons	• CALCRL:RAMP1:RCP	• goblet cells • cDCs/dDCs • T cells • ILC2s • neutrophils • macrophages	• regulate mucus production and M cells in the gut • promote IL-23 production by dDC • suppress type-2 inflammation in the lungs • increase intestinal inflammation • modulate neutrophil and macrophage response to bacteria (lung, skin, and meninges) • limit immune response to UVB skin damage • regulate defense against pathogens (STm, *C. albicans*, *C. difficile*, *S. aureus*, *S. pyogenes*, *S. pneumoniae*)
NMU	*Nmu*	• ChAT$^+$ enteric neurons • Undefined lung neurons	• NMUR1 • NMUR2	• ILC2s (NMUR1)	• increase type-2 inflammation in the lung and gut
VIP	*Vip*	• TRPV1$^+$ neurons • Enteric neurons	• VPAC1 • VPAC2 • PAC1	• ILC3s (VPAC1, VPAC2) • CD4$^+$ T cells (VPAC2)	• promote gut barrier integrity and nutrient absorption • regulate immune response to *C. rodentium* • promote type-2 inflammation in the lungs
TAFA4	*Tafa4*	• GINIP$^+$ neurons	• FPR1 • alternative receptor/ mechanism that remains to be defined	• dermal macrophages (receptor unknown)	• limit UVC-induced skin inflammation
Glutamate	N/A	• MRGPRD$^+$ neurons	• GluK2/K5	• mast cells	• reduce skin inflammation
Acetylcholine (invertebrates)	N/A	• *C. elegans* – Enteric neurons • *D. melanogaster* – ARCENS	• mAchR family • nAchR family	• gut epithelial cells	• promote WNT signaling and defense against *S. aureus* • promote resolution of gut inflammation

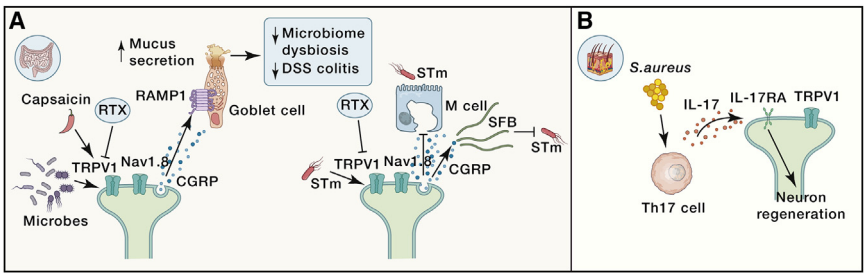

Figure 2. Neuroimmune signaling in tissue homeostasis

(A) Sensory neurons drive homeostasis in the gut. (B) Immune cells' crosstalk with microbes promotes sensory neuron growth during wound healing.

cell) and the presence of a diverse yet select flora of gut microbes are important for barrier homeostasis and exclusion of pathogens. Future work characterizing the mechanisms by which human peripheral neurons sense and respond to gut flora dysregulation will greatly improve our understanding of these complex multi-system and multi-organismal processes.

The skin is the body's largest and outermost organ, and homeostatic maintenance of this physical barrier is the most fundamental defense against exogenous threats. The skin, like other barrier tissues, is densely innervated by sensory neurons and colonized by a diverse microbiome that we are now beginning to appreciate for its contributions to tissue homeostasis and inflammation. In a full-thickness wound healing model, it was observed that colonization with *S. aureus* improved neuronal regrowth following injury.[57] *S. aureus* promoted the accumulation of interleukin-17 (IL-17)-producing T helper cells (Th17) in the skin, where they interacted with cutaneous nociceptors. Upon skin damage, tissue-resident Th17 cells became activated by the infiltration of commensal *S. aureus* and began to produce IL-17. This response did not impact host defense against *S. aureus* infection. Rather, IL-17 facilitated regrowth of TRPV1$^+$ neurons.[57] Ablation of either Th17 cells or IL-17RA receptors on TRPV1$^+$ neurons was sufficient to interrupt this pathway, demonstrating that *S. aureus*-responsive Th17 cells promoted neuronal regrowth to reestablish homeostasis following skin injury (Figure 2B). This pathway is an excellent example of two themes that will continue to arise throughout this review: (1) communication between coevolved nervous and immune systems during health and disease and (2) the interconnectedness of these systems with commensal microbes that have evolved alongside the host.

Recent studies have investigated the role of skin-innervating sensory neurons in ultraviolet (UV) radiation-induced damage. It was found that acute UV-C exposure, in a murine model of sunburn, activated a subset of non-peptidergic sensory neurons defined by their expression of GINIP$^+$.[13] Ablation of these neurons by a GINIP-DTR system resulted in more severe and persistent inflammation and disease pathology. Tim4$^+$ dermal macrophages are found in close proximity to GINIP$^+$ neurons in skin. Activated GINIP$^+$ neurons produced the neuropeptide TAFA4, which limited UV-C-mediated inflammation by supporting the survival and IL-10 production of neighboring Tim4$^+$ dermal macrophages. The effects of TAFA4 in this model were independent of the previously identified receptor FPR1, implicated in TAFA4-mediated chemotaxis.[40] The receptor by which TAFA4 signals in this pathway remains to be defined. Experiments investigating the role of peptidergic neurons during UV-B-mediated skin damage found that TRPV1$^+$ neurons and the neuropeptide CGRP suppressed UV-mediated cutaneous inflammation.[58] In this model, chemical ablation of TRPV1$^+$ neurons and genetic ablation of *Calca* both augmented the abundance of dermal DCs and αβ-T cells in the UV-B-exposed footpad. While expression data suggest that *Ramp1* is expressed by dendritic cells (DCs) and T cells, the obligate responders to CGRPα and the roles of these immune cells remain to be defined in this model.[58] Together, these studies illustrate how distinct sensory neurons not only promote pain and hypersensitivity following UV damage but also release unique neuropeptides to suppress local inflammation in favor of tissue repair. Whether we focus on the skin or the gut, it is abundantly clear that communication between neurons and peripheral tissues is key to establishing and maintaining homeostatic conditions as well as appropriate immune responses.

NEUROIMMUNE AXIS DRIVES AUTOINFLAMMATION AND ALLERGY

Clinical evidence of neuronal contributions to autoinflammatory skin pathology has been observed when patients with traumatic spinal transection or nerve ligation exhibit clearance of plaque psoriasis, atopic dermatitis, and other inflammatory skin conditions in denervated skin.[3,59–61] Epidural nerve block with lidocaine and local injections with botulinum neurotoxin have both proven efficacious in treating plaque psoriasis, further highlighting the importance of neuronal function for this disease pathology.[62–64] Elevated plasma concentrations of CGRP and SP, as well as increased DC expression of the CGRP receptor in psoriatic plaques suggest that these neuropeptides may mediate neurogenic inflammation and cutaneous pathology.[62,65–67] Together, these clinical observations imply the importance of sensory innervation for cutaneous autoinflammatory pathologies in the clinic and highlight the broader ability of sensory neurons to act as local immune effectors by the release of immunologically active neuropeptides.

Genetic and pharmacologic murine models of psoriasis have recapitulated clinical observations. Both chemical ablation of TRPV1$^+$ nociceptors and surgical denervation attenuated inflammation and disease pathology in the imiquimod (IMQ) and the KC-Tie2 models of psoriasis. Plaque psoriasis is an autoinflammatory/autoimmune skin disease with a complex pathology, characterized by an early type I interferon signature, dysregulation of the skin IL-23/IL-17 axis, and epidermal scaling and thickening.[68–71] Although the precise etiology of this disease is not fully characterized, the efficacious clinical use of biologics targeting IL-23 and IL-17 reveal the importance of this axis for disease pathology.[72] In the murine model of IMQ-induced psoriasiform inflammation, TRPV1$^+$ sensory neurons were necessary for the induction of *Il23a* by CD301b$^+$ dermal dendritic cells (dDCs)

and downstream type-17 inflammation, thus highlighting a potential mechanism by which sensory neurons may mediate innate immune activation and disease in patients. Recent work has demonstrated that neurons can sense IMQ via direct gating of TRPA1 channels and may, in turn, act on local DCs by multiple effector mechanisms including CGRP and chemokine release as well as contact-mediated DC activation.[73] Using an optogenetic model of repeated nociceptor activation, it was demonstrated that TRPV1$^+$ neurons are not only required but that their activation is also sufficient to induce type-17 psoriasiform inflammation by a CGRP-dependent pathway. Repeated optogenetic activation of cutaneous TRPV1$^+$ neurons resulted in visually obvious increased ear thickness, erythema, and scaling as well as induction of local *Il23a*, *Il17a*, and neutrophil recruitment.[74] These findings may lead us to presume that the release and signaling of CGRP participate in the dysregulation of the IL-23/IL-17 axis in human disease, but robust data demonstrating that antagonism of CGRP fully recapitulates TRPV1$^+$ neuron ablation remain to be shown in other murine models of the disease or in clinical studies. While CGRP agonism has been shown to rescue the production of *Il23a* in TRPV1$^+$-neuron-ablated mice, antagonism of the CGRP receptor was not sufficient to recapitulate the reduction of *Il23a* observed in the absence of nociceptors.[75] However, in other work, CGRP antagonism attenuated acanthosis and skin thickening in the IMQ model of psoriasis, a finding that is consistent with *in vitro* studies that have demonstrated the ability of CGRP to directly promote keratinocyte proliferation.[62,76] Together, these data suggest the existence of multiple decoupled pathways by which cutaneous sensory neurons act on the IL-23/IL-17 axis in the skin and drive hyperkeratosis during plaque psoriasis. The CGRP/IL-23/IL-17 axis remains a hot topic of discussion and research, with implications for host immunity that will be discussed later in this review.

CGRP is not the only neuropeptide stored in dense core vesicles in nerve terminals and secreted into the periphery by cutaneous sensory neurons. SP, encoded by the pre-pro/tachykinin (*Tac1*) gene, is also released by activated TRPV1$^+$ nociceptors. Multiple studies have demonstrated that intradermal (i.d.) injections of SP are sufficient to induce rapid and non-specific local inflammation in the form of edema, increased vascular permeability, granulocyte recruitment, and increased leukocyte adhesion to the vascular endothelium. These responses, however, were abrogated when SP was injected into the skin of mast-cell-deficient mice, demonstrating that this innate response was mediated by local mast cell activation/degranulation.[77,78] The disease implications of SP acting on mast cells are most pronounced in models of atopic dermatitis (AD). AD is a prevalent skin condition characterized by pruritis and type-2 inflammation. Many enzymatically active allergens and inflammatory agents have been shown to produce an action potential in sensory neurons and drive neuropeptide release. For example, house dust mite (HDM), a common environmental allergen used to model AD in mice, directly activated TRPV1$^+$ neurons via intrinsic cysteine protease activity. In this model, SP, released by activated TRPV1$^+$ neurons, was shown to act on local mast cells to promote degranulation via ligation of the mast-cell-specific MRGPRB2 receptor. In the absence of MRGPRB2, clinical scoring and type-2 inflammation were both attenuated in this HDM model of AD[79] (Figure 3A). How this specific pathway may become dysregulated in human disease remains to be elucidated. However, elevated serum SP has been observed in patients with AD and correlated with disease severity.[80,81]

Insufficient steady-state regulation of mast cells may also play a role in cutaneous autoinflammatory diseases. In mice, a subset of polymodal C-fiber neurons express MAS-related GPR member D (MRGPRD$^+$).[82] These MRGPRD$^+$ neurons suppress mast cell function, reduce the expression of activating receptors such as MRGPRB2, and ultimately maintain homeostasis in the skin.[83] Interestingly, it was shown that long-term ablation of Langerhans cells (LCs) reduced the abundance of MRGPRD$^+$ neurons in the epidermis and conferred augmented mast cell response to the contact irritant croton oil. MRGPRD$^+$ neurons release the neurotransmitter glutamate, which, via ionotropic GluK2/K5 glutamate receptors, altered the mast cell transcriptional state and suppressed mast cell function (Figure 3A). Negative regulators of mast cell function such as this may also be dysregulated in inflammatory skin conditions such as AD. Taken together, these studies highlight a unique circuit by which the nervous and immune systems coregulate and define the reactivity of mast cells in the skin.

In the papain model of AD, SP mediated cutaneous inflammation via a mast-cell-independent mechanism. Papain, the enzymatically active allergen found in papaya, can induce a mixed itch/pain response through activation of proteinase-activated receptors (PARs) expressed by sensory neurons and/or through receptor-independent mechanisms.[16,84] Consequently, papain-activated sensory responses and inflammation were significantly attenuated in the absence of TRPV1$^+$ neuron activation. Mechanistically, SP released from TRPV1$^+$ neurons signaled through the MAS-related GPR, member A1 (MRGPRA1) receptor on dermal DC2s (dDC2) to promote migration to the draining lymph nodes, where they primed a Th2 response characteristic of this model[16] (Figure 3A).

These examples demonstrate the evolution of neuronal subsets (e.g. TRPV1$^+$SP$^+$ neurons vs. Mrgprd$^+$glutamate$^+$ neurons) that differentially regulate the function of immune cells in the skin. Additionally, the immune system is able to integrate a common neuronal stimulus (SP) into multiple distinct responses that serve a common end (innate and adaptive type-2 immune activation). These parallel mechanisms illustrate that the strength and complexity of an evolved host defense are intrinsic to the system and proportionally detrimental and complex when dysregulated during autoinflammation.

The lungs form the interface between air and the bloodstream, and this barrier is exposed to airborne irritants including microbial pathogens, environmental pollutants, and allergens. The lungs are innervated mainly by vagal sensory neurons whose cell bodies are found in the nodose ganglia[85] (Figure 1B). Several studies have now revealed that neurons regulate allergic immune responses in the lungs, and targeting neurons could have therapeutic potential to treat asthma.[86,87] In mouse models of type-2 airway inflammation, exposure to allergens such as ovalbumin (OVA) and HDM caused the production of IL-5 by lung immune cells. Researchers found that nociceptors detected IL-5 and responded by releasing VIP, which then stimulated T cells and innate lymphoid cells (ILCs) to drive inflammation. Ablation or targeting of NAV1.8$^+$ sensory neurons with the charged lidocaine

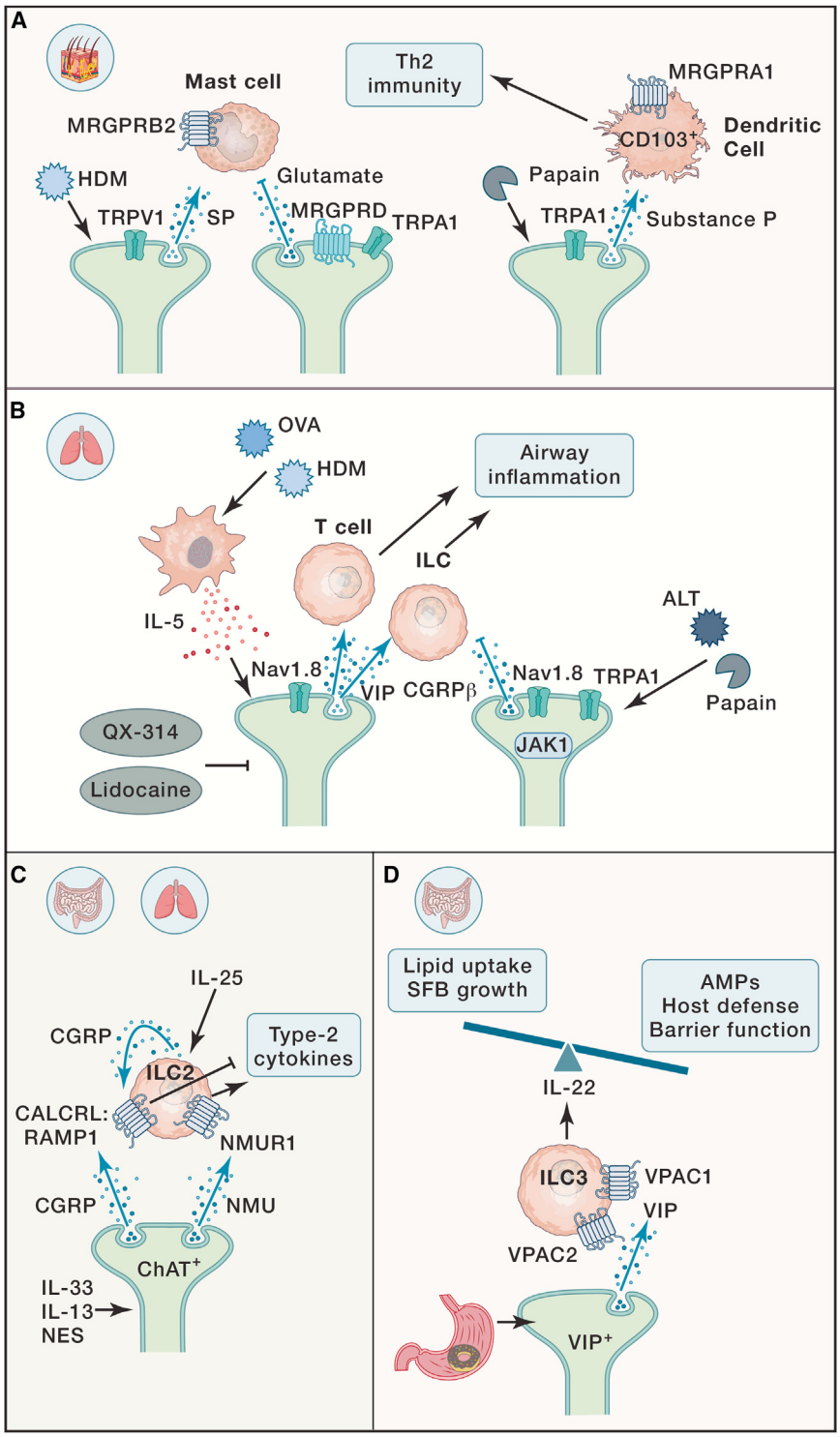

Figure 3. Neuroimmune communication regulates autoinflammation and allergy

(A) SP$^+$ peptidergic neurons and glutamate$^+$ non-peptidergic neurons antagonistically regulate mast cell reactivity in the skin. Independent of mast cells, SP also drives dendritic cells to promote a Th2 response at the dLN.

(B) Sensory neurons regulate lung inflammation through the neuropeptides VIP and CGRPβ.

(C) Neuropeptide NMU promotes a type-2 innate immune response in the lung and gut by activating ILC2s that are constrained by neuronally derived and autocrine CGRP.

(D) Feeding promotes the release of VIP from enteric neurons. VIP acts on IL-22$^+$ ILCs and regulates the balance between nutrient uptake and barrier defense.

derivative QX-314 attenuated allergen-induced airway inflammation in mice in OVA- and HDM-sensitized mice (Figure 3B). Interestingly, QX-314 treatment had little effect in an OVA-induced asthma mouse model, suggesting that the impact of nociceptors on lung inflammation varies across different models.[88]

Distinct neuropeptides can also have opposing effects on type-2 inflammation in the lungs. While the neuropeptide VIP may drive allergic responses, a recent study revealed a contrasting role for CGRPβ. Neuron responses to type-2 cytokines are regulated by signaling through Janus kinases such as JAK1. Mice with a gain-of-function variation of JAK1 in vagal sensory neurons exhibited increased production of CGRPβ. This neuropeptide suppressed ILC function and limited allergic lung inflammation induced by the fungal allergen *Alternaria alternata* (ALT). In this setting, targeting TRPV1$^+$ vagal neurons by intraganglionic resiniferatoxin injection reduced allergic responses to ALT. Additionally, conditional knockout of *Jak1* in NAV1.8$^+$ neurons limited lung inflammation caused by ALT and the protease allergen papain[89] (Figure 3B). These examples highlight the context-dependent impact of sensory neurons on promoting either lung allergy or tissue homeostasis. How different allergens stimulate lung nociceptors to produce either VIP or CGRPβ remains to be defined.

The neuropeptides NMU and CGRP have recently been shown to play antagonistic roles in amplifying/constraining mucosal immunity. Type-2 inflammation at mucosal surfaces is regulated by the release of alarmins such as IL-25 and IL-33, followed by rapid activation of local group 2 (ILC2s).[90–92] This alarmin-mediated pathway to ILC2 activation and type-2 inflammation is common to murine models of allergic asthma (i.e., HDM), type-2 inflammation in the gut (i.e., gastric Ova), and anti-helminth immunity (i.e., *Nippostrongylus brasiliensis* [*N. brasiliensis*]). Interestingly, one of the hallmark transcripts enriched in barrier tissue ILC2s compared with other ILCs was *Nmur1*, which encodes the type-1 receptor for NMU

(NMUR1).[29,93,94] Consistent with this expression pattern, ILC2s have been shown to colocalize with NMU$^+$ neurons in the lung and NMU$^+$ cholinergic (ChAT$^+$) enteric neurons in the gut.[29,93,94] *In vitro* and *in vivo* experiments have collectively demonstrated that NMU$^+$ enteric neurons can sense and respond to the alarmin IL-33, the type-2 cytokine IL-13, and *N. brasiliensis* excretory/secretory products (NES), highlighting multiple mechanisms by which neurons may detect helminth infection or local type-2 inflammation (Figure 3C).[29,93] By *in vitro* ILC2 stimulation experiments and *in vivo* alarmin-mediated inflammatory models, NMU was sufficient to promote ILC2 proliferation and type-2 cytokine production, although the greatest response to NMU was observed when combined with IL-25 and, to a lesser extent, IL-33, suggesting that NMU may potentiate the effects of alarmins on ILC2s.[29,93,94] Consistent with this paradigm, i.n. IL-25 and NMU was sufficient to drive type-2 cytokine (IL-5 and IL-13) production in the lung as well as eosinophilia, histopathologic signs of inflammation and airway hyperresponsiveness (AHR) in mice.[93] This response in the lung was thought to be driven in part by NMU-/IL-25-mediated expansion of responding ILC2s. The combination of NMU and IL-25 *in vivo* nearly doubled the frequency of proliferating ILC2s observed in the lung by single-cell RNA sequencing (scRNA-seq) and preferentially expanded IL-25-responsive (IL-17RB$^+$) ILC2s. Similarly, intraperitoneal (i.p.) injections of NMU into *Il1rl1*$^{-/-}$*Il17rb*$^{-/-}$ and wild type (WT) mice demonstrated that NMU is sufficient to drive the expansion of ILC2s in the gut, but the *in vivo* induction of type-2 cytokines by NMU may require responsiveness to IL-33 and IL-25 as well.[29] Indeed, in the HDM model, *Nmu*-ablated mice failed to expand this population and drive IL-5 and IL-13 expression in ILC2s when compared with WT counterparts.[95] Consistent with findings in the lung during type-2 autoinflammation, *Nmur1* expression by ILC2s was shown to be required for robust type-2 anti-helminth immunity during *N. brasiliensis* infection, evidenced by increased *N. brasiliensis* burden in the lung and gut.[29] Taken together, these studies outline a pathway in which lung-innervating neurons are activated by helminth products and local type-2 inflammation and augment alarmin-mediated ILC2 expansion and cytokine production by NMU release and NMU/NMUR1 signaling (Figure 3C). The significance of this pathway as a mediator of human disease is supported by the finding that IL-25 and NMU are sufficient to drive a transcriptional signature in ILC2s comparable to that in human allergic asthmatics.[93,96–100]

By contrast, CGRP has been found to act as a negative regulator of ILC2 function in a gastric OVA model of type-2 inflammation.[101] In this model, it was observed that the CGRP-coding *Calca* transcript is enriched in expanding and activated ILC2s. In contrast, *Ramp1* and *Calcrl*, which encode the CGRP receptor, were highly expressed by ILC2s at steady state but were downregulated during OVA-mediated inflammation. *Ex vivo* stimulation of ILC2s revealed that IL-25 can directly upregulate the expression of *Calca* in these cells, and *in vivo* experiments using *Calca*-ablated mice demonstrated that IL-25-mediated ILC2 proliferation and gut inflammation are unrestrained in the absence of endogenous CGRP.[101] These findings translate to a potential autocrine loop in which IL-25-activated ILC2s produce and respond to the regulatory neuropeptide CGRP (Figure 3C). Similarly, global ablation of *Calca* or deletion of *Ramp1* from the immune compartment was sufficient to promote augmented host defense to infection by the helminth *N. brasiliensis*, reducing worm burden in the lung and gut.[29,94,102] While *Calca* was lowly expressed in ILC2s at steady state, neighboring ChAT$^+$ neurons in the gut have been shown to constitutively express the neuropeptide and may also contribute to this regulatory pathway as an early negative effector.[101] Consolidating the tremendous amount of work put into this pathway, we find a shared ILC2/NMU/CGRP axis across the lung and gut that tightly regulates ILC2-mediated type-2 inflammation. The conservation of this pathway across the lung and gut may suggest that it evolved specifically to defend the host from helminths such as *N. brasiliensis*. If this is the true, it is remarkable to think about the number of regulatory mechanisms that take part in this pathway to promote robust immunity while preventing dysregulated inflammation.

Group 3 ILCs (ILC3s) are an important source of interleukin-22 (IL-22) in the intestine and, by its production, participate in gut homeostasis and immunity.[103,104] Multiple recent studies have focused on the role of VIP on ILC3s in the gut. Among intestinal ILC3s, it was observed that one subset (CCR6$^+$), enriched in tertiary lymphoid structures, expressed VPAC2 (*Vipr2*) and colocalized with VIP$^+$ enteric neurons.[105] Ablation of the VPAC2-coding *Vipr2* under the control of *Rorc* augmented the production of IL-22 by ileal ILC3s. At steady state, *Vipr2*-ablated mice demonstrated increased frequencies of IL-22$^+$ ILC3s in the gut and enhanced intestinal barrier integrity as evidenced by increased epithelial expression of the antimicrobial peptide *RegIII*γ, lengthened crypts and villi, as well as increased frequency of proliferating crypt cells. Chemogenetic experiments utilizing activating or inhibitory DREADDS further supported the ability of VIP$^+$ enteric neurons to release VIP and inhibit IL-22 production by ILC3s (Figure 3D).

During GI infection with *Citrobacter rodentium* (*C. rodentium*), suppression of VIP$^+$ neurons protected the host from death and prevented *C. rodentium* translocation to other organs. This highlights a unique mechanism by which VIP$^+$ neuron activation inhibits host defense. However, consistent with the finding that VIP is rapidly released following the ingestion of food, the authors found that VIP-mediated suppression of ILC3s was necessary for the uptake of fats across the gut epithelium.[106] Activation of the VIP/ILC3/IL-22 axis during feeding also promoted unique changes to the gut flora, characterized by an increased ratio of *Firmicutes* to *Bacteroides* and lengthening of filaments on SFB. These findings illustrate a novel pathway by which the VIP/ILC3/IL-22 axis promotes barrier integrity and host defense during times of fasting and increased permeability and nutrient transport when feeding. Conversely, it is important to note that others have reported that feeding and VIP promote IL-22 production by ILC3s *in vivo* and confer phenotypes opposite to those described. In one set of studies, broad and specific ablation of *Vipr2* on ILC3s reduced the frequency of IL-22$^+$ ILC3s in the gut and worsened disease during a DSS-colitis model, suggesting that VIP-mediated IL-22 production was necessary for barrier integrity[107] (Figure 3D). Others found that VIP was necessary for ILC3 recruitment to the gut via VPAC1 signaling and host defense during *C. rodentium* infection.[108] These contradictory findings suggest

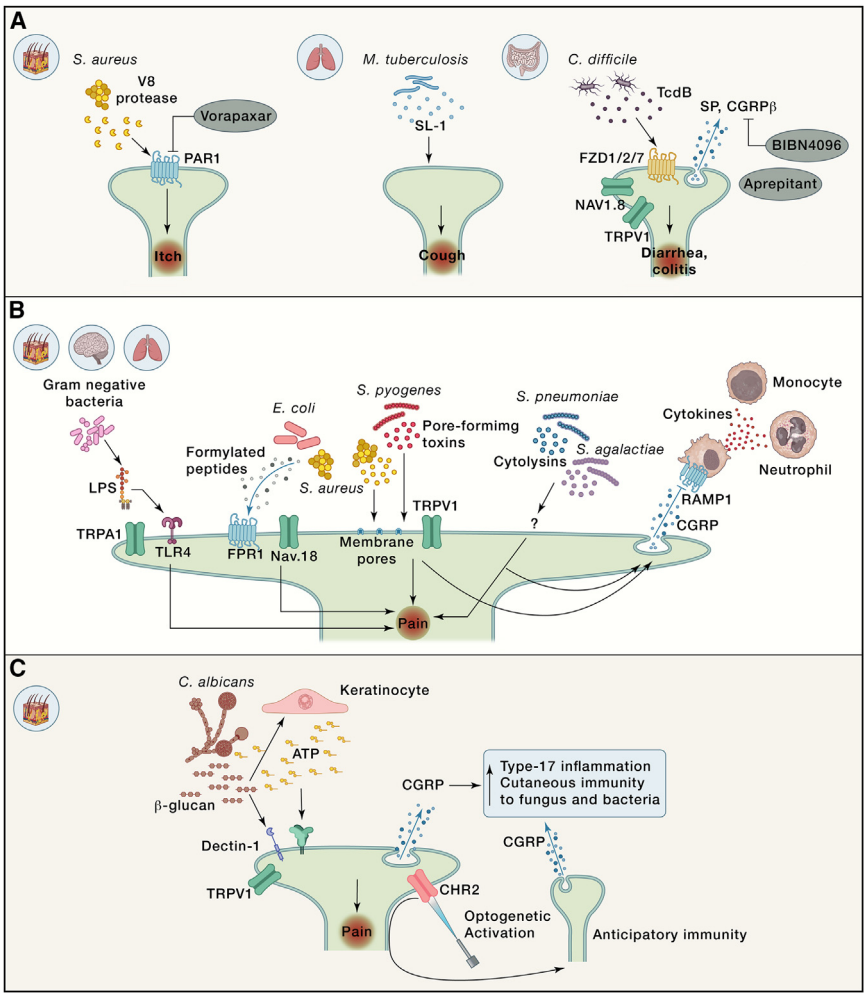

Figure 4. Neurons crosstalk with microbes and immune cells in host defense

(A) Sensory neurons are directly activated by bacterial toxins and drive behavioral reflexes.

(B) Bacteria can hijack neuroimmune signaling to induce pain and limit inflammation.

(C) TRPV1$^+$ neurons enhance cutaneous immune responses to pathogens and promote anticipatoryimmunity in adjacent skin regions.

that the VIP/ILC3/IL-22 axis is highly complex and likely under the regulation of additional factors that remain to be defined. Nonetheless, these reports together demonstrate a unique model of neuron-microbe-immune crosstalk that differentially regulates gut barrier integrity in concordance with the host's needs (i.e., feeding or host defense).

NEURON-MICROBE-IMMUNE CROSSTALK REPRESENTS A COMPLEX ARMS RACE IN HOST DEFENSE

Several studies have identified specific bacterial factors that can directly activate sensory neurons to drive behavioral reflexes. For example, *S. aureus*, a bacterium that frequently colonizes itchy and inflamed skin lesions in patients with AD,[109,110] was recently shown to directly induce itch and scratching. During epicutaneous *S. aureus* exposure, bacteria produced the serine protease V8, which was both necessary and sufficient to drive scratching. Mouse and human DRG neurons express the V8 receptor, proteinase-activated receptor 1 (PAR1), and were directly activated by the bacterial protease. Mice with TRPV1$^+$ neurons deficient in PAR1 exhibited reduced itch during exposure to *S. aureus*, and targeting PAR1 with small interfering RNA (siRNA) or a pharmacological antagonist could block *S. aureus*-induced itch[111] (Figure 4A). *S. aureus* exposure resulted in skin inflammation and damage to the skin barrier (as measured by transepidermal water loss), and scratching worsened skin pathology and exacerbated skin damage beyond the bacterial inoculation site. It would be interesting to determine whether scratching could enhance *S. aureus* pathogenesis by promoting the penetration of the bacterium into deeper tissues or spread to distant sites or to naive hosts.

Mycobacterium tuberculosis (Mtb) lung infections are characterized by chronic cough. The Mtb cell wall contains many lipids and glycolipids including the sulfated metabolite Sulfolipid-1 (SL-1). Mtb cell wall extract can activate mouse nodose/jugular ganglia neurons and human and mouse DRG neurons, while extracts from Mtb strains deficient in SL-1 did not induce calcium influx in neurons. In a guinea pig model of cough, treatment with nebulized Mtb cell wall extract or purified SL-1 was sufficient to induce coughing behaviors[112] (Figure 4A). Although SL-1 is one of the most abundant lipids produced by Mtb, a role for SL-1 in promoting virulence has not been described. Mtb strains lacking SL-1 are not attenuated in lung infection models and exhibit enhanced resistance to killing by macrophages. The purpose of SL-1 in Mtb pathogenicity may be to activate neurons and drive a nocifensive reflex to facilitate the transmission phase of infection.

In the gut, nociceptors drive a number of protective reflexes including visceral pain and diarrhea. *Clostridioides difficile* (*C. difficile*) is a leading cause of gastrointestinal infection characterized by painful cramping and bloody diarrhea. The TcdB toxin is a major *C. difficile* virulence factor that can utilize several different receptors to enter cells including frizzled-1, -2, and -7 (FZD1/2/7). Recently, it was shown that enteric sensory neurons express *Fzd1*, *Fzd2*, and *Fzd7* and could be activated by TcdB. TcdB activation of NAV1.8$^+$ TRPV1$^+$ extrinsic gut-innervating sensory neurons induced SP release, and both *Tac1* knockout mice and mice lacking NK1R (the receptor for SP) exhibited protection from *C. difficile* infection. Furthermore, expressing the enzymatic domain of TcdB in *Tac1*$^+$ gut-innervating neurons induced diarrhea in mice. In addition to identifying a role for

SP, the authors of this study identified a role for CGRPβ signaling in TcdB-induced pathology. This neuropeptide was also elevated in mice exposed to TcdB, and *Calcb* knockout mice exhibited decreased disease from both TcdB treatment and *C. difficile* infection. Treating mice with the NK1R antagonist aprepitant or the CGRP receptor antagonist BIBN4096 reduced inflammation and *C. difficile* bacterial burden[19] (Figure 4A). In this study, pericytes were also found to play a role in driving neurogenic inflammation during *C. difficile* infection. However, the precise mechanism for pericyte-mediated pathology was not determined. This study highlights that while there have been many advances in our understanding of the importance for signaling between neurons and immune cells, there is still a continued need for investigation into how sensory neurons crosstalk with stromal cells to regulate innate immunity and host defense.

A common symptom of microbial infections is pain, and numerous studies have shown that pathogens can induce pain to hijack neuroimmune signaling and evade innate immunity (Figure 4B). For example, the outer membrane of gram-negative bacteria contains lipopolysaccharide (LPS), which is shed during infection. LPS is a potent trigger of inflammation and is well known to activate multiple immune cell types including macrophages and neutrophils by stimulating TLR4 signaling. Sensory neurons also express the TLR4 receptor and can detect LPS. LPS/TLR4 signaling on TRPV1$^+$ nociceptors drives TRPA1-dependent neuronal activation, pain evidenced by nocifensive behavior, and release of the neuropeptide CGRP.[113,114] Neurons also express receptors for *N*-formyl peptides, which are actively released by bacterial pathogens during infection. NAV1.8$^+$ DRG neurons express the receptor FPR1 and can respond to the formylated peptides fMLF from *Escherichia coli* and fMIFL from *S. aureus*.[115,116] Furthermore, *S. aureus* produces cytolytic toxins α-hemolysin (Hla), γ-hemolysin (bi-component leucocidin HlgAB), and phenol-soluble modulin α3 (PSMα3), all of which drive calcium flux and action potentials in sensory neurons. Although all these toxins activate sensory neurons *in vivo*, only Hla was necessary for a spontaneous pain response during *S. aureus* paw injection.[117] Interestingly, ablation of sensory neurons by a NAV1.8-Cre/DTA system not only attenuated pain during subcutaneous footpad infection but also augmented local innate immunity by improved neutrophil/monocyte recruitment and draining lymph node cellularity.[115] Consistent with this model, it was recently demonstrated that TRPV1$^+$ neurons and the neuropeptide CGRP attenuated innate immunity to subcutaneous *S. aureus* infection. This was mediated by the suppression of neutrophil recruitment and polarization of local macrophages to an M2-like phenotype.[118] These findings suggest that while neurons can sense *S. aureus*, their activation in this setting might be counterproductive to the host by decreasing myeloid cell responses and instead represents an adaptation of the microbe to promote its survival.

Streptococcus pyogenes (*S. pyogenes*) is an invasive bacterial pathogen and most common causative agent of necrotizing skin infections where "pain out of proportion" to tissue damage is a distinguishing early symptom. In a murine subcutaneous *S. pyogenes* infection model, TRPV1$^+$-neuron-ablated mice showed improved innate immunity to this bacterium. TRPV1$^+$ neurons suppress neutrophil recruitment and antimicrobial clearance in skin and soft tissues. Local injections with botulinum neurotoxin A (BoNT/A), which blocks neuropeptide release, and treatment with the small molecule CGRP receptor antagonist BIBN4096 both phenocopy TRPV1$^+$ neuron ablation, suggesting that CGRP is responsible for this immune suppression. CGRP was found to inhibit neutrophil killing of *S. pyogenes in vitro*.[119] Together, these pathways highlight the ability of invasive pathogens to hijack neuronal activation and neuropeptide release to suppress subcutaneous innate immunity.

Nociceptors also detect microbial factors during lung infections (Figure 4B). TRPV1$^+$ sensory neurons were found to suppress host defense in a mouse model of bacterial pneumonia. During lethal intratracheal inoculation of bacteria, TRPV1$^+$ neurons released CGRP, which was immunosuppressive and attenuated clearance of pathogens from the lungs. Depleting TRPV1$^+$ neurons reduced bacterial burden during *S. aureus* lung infection, improved core body temperature maintenance, and increased survival. It also significantly reduced core body temperature drop in response to *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (*P. aeruginosa*) pneumonia. Nociceptor-deficient mice exhibited increased proinflammatory-cytokine production during lung infection and increased neutrophil and γδ T cells in the lungs. Therefore, targeting nociceptors or CGRP may be worthwhile approaches to improve immune responses for treating bacterial pneumonia.[95]

The structures of the CNS are surrounded by the meninges, which form a protective barrier for the brain and the spinal cord. The cerebral meninges are innervated by sensory neurons whose cell bodies reside in the TG. Pain, in the form of a severe headache, is a cardinal symptom of bacterial meningitis. A recent study demonstrated that TG nociceptors are activated by the meningeal pathogens *Streptococcus pneumoniae* and *Streptococcus agalactiae* (Figure 4B). These bacteria induced calcium influx when applied to cultured TG neurons, and this response was reduced when neurons were treated with mutant *S. pneumoniae* lacking the pore-forming toxin pneumolysin or with *S. agalactiae* deficient in the cytolytic toxin β-hemolysin. Upon activation, NAV1.8$^+$ nociceptors released CGRP, which stimulated meningeal macrophages via RAMP1. CGRP polarized the transcriptional responses of macrophages to infection both *in vitro* and *in vivo*, with lowered expression of cytokines and chemokines including tumor necrosis factor (TNF) and CXCL1. This led to attenuated neutrophil and monocyte recruitment to the meninges during infection. Treatment with CGRP antagonist BIBN4096 reduced bacterial invasion into the brain. Furthermore, conditional knockout of *Ramp1* in meningeal macrophages increased macrophage chemokine expression during infection and made mice less susceptible to bacterial meningitis.[120] The results show that in the meninges, like other host barriers, bacterial pathogens can employ strategies to hijack neuronal polarization of the innate immune response to promote infection.

Based on these examples of nociceptors suppressing host defense, targeting sensory neurons represents a potential therapeutic avenue to treat bacterial infections. However, recent studies have also demonstrated seemingly contradictory roles for these neurons and neuropeptides in more superficial tissues. *C. albicans* is a dimorphic fungus and a natural part of the human flora that can cause dangerous mucosal and systemic

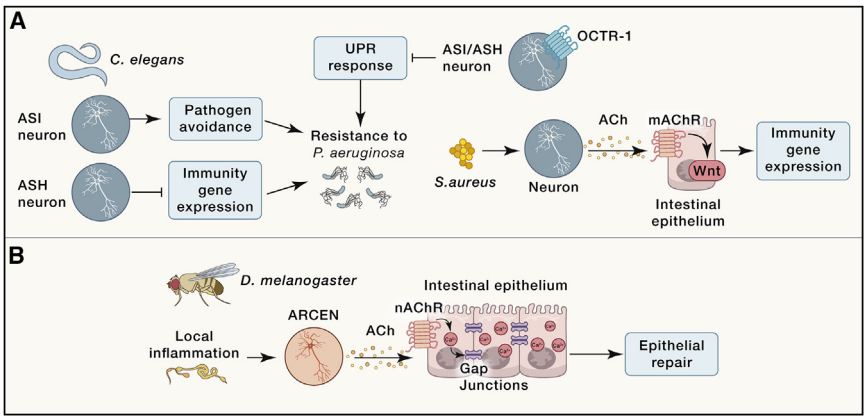

Figure 5. Neuronal control of immunity is evolutionarily conserved

(A) Sensory neurons promote defense against pathogens in *C. elegans*.

(B) Neurons regulate tissue repair in the *D. melanogaster* gut.

infections in immunocompromised patients. Innate immunity to *C. albicans*, in both mice and humans, depends on the detection of the invading pathogen—ligation of Dectin-1 on host immune cells by β-glucan on the yeast surface. This is evidenced in a family of four women who suffered from recurrent mucocutaneous *C. albicans* infections as a result of a shared genetic mutation creating an early stop codon in the Dectin-1 gene.[121] *Ex vivo* experiments with human DCs demonstrated that β-glucan directly drives the production of IL-23 and highlights the IL-17/IL-23 axis that cutaneous antifungal immunity shares with plaque psoriasis. Indeed, in a murine model of epicutaneous *C. albicans* infection, IL-23 from dDCs and IL-17 from γδ T cells were necessary for the recruitment of neutrophils and fungal clearance.[122] Consistent with murine models of psoriasis, ablation of TRPV1$^+$ neurons significantly diminished the host's ability to induce *Il23a* and mount a robust type-17 immune response clearing *C. albicans*. Sensory neurons are capable of detecting *C. albicans* by (1) ligation of neuronal Dectin-1 by fungal b-glucan, (2) neuronal activation by ATP released from keratinocytes whose Dectin-1 has been ligated by b-glucan, and (3) detection of ATP directly produced by *C. albicans*[123–125] (Figure 4C). However, it is currently unclear which mechanism of activation is necessary for cutaneous antifungal immunity. Nonetheless, one effector mechanism by which nociceptors mediate antifungal immunity has been rigorously characterized. Experiments utilizing local CGRP antagonist ($CGRP_{32–37}$) revealed that the neuropeptide CGRP is necessary for antifungal type-17 immunity and the induction of *Il23a*. This demonstrates that CGRP is likely the means by which sensory neurons regulate the IL-23 axis. This hypothesis is supported by experiments demonstrating that recombinant rat CGRP rescues *Il23a* levels and antifungal type-17 immunity in TRPV1$^+$-neuron-ablated mice. Together, these data suggest that TRPV1$^+$ sensory neurons mediate IL-23 production and antifungal immunity via the secretion and activity of CGRP. Furthermore, repeated optogenetic activation of cutaneous nociceptors (a model previously highlighted in our discussion of autoinflammatory skin diseases) conferred improved innate immunity to both epicutaneous *C. albicans* and *S. aureus*, which was abolished by the antagonism of CGRP. Remarkably, type-17 inflammation and host defense are augmented at both the site of optogenetic activation and in adjacent (non-photostimulated) infected regions. Use of bupivacaine, an anesthetic that inhibits nociceptor activation without impacting neuropeptide release, attenuated the adjacent inflammatory response, suggesting that the distal inflammation depends on the generation of a reflex arc rather than the spread of neuropeptides from the site of neuronal activation (Figure 4C). These results define a unique mechanism by which TRPV1$^+$ neurons sense invasive pathogens in the skin and drive anticipatory immunity by the release of CGRP in surrounding tissues.[126]

Ultimately, each of these models provides insights into the different effector functions of sensory neurons in the skin. Together, these findings raise additional questions about how TRPV1$^+$ neurons regulate skin immune responses. How and why do TRPV1$^+$ neurons and the neuropeptide CGRP promote inflammation and bacterial clearance in superficial skin infections when these same effectors suppress host defense in deeper subcutaneous tissues and in the lungs? What other cues from the surrounding tissue environment contribute to context-dependent immune responses, and does this apparent compartmentalization reflect unique adaptations that benefit the host or the bacterium? Furthermore, if CGRP is necessary for *Il23a* and type-17 immunity in this setting, why is this less apparent in type-17 psoriasiform inflammation? We have no doubt that the field of neuroimmunology will soon offer up exciting and unique answers to these questions and more.

SENSORY NEURONS ARE EVOLUTIONARILY CONSERVED MEDIATORS OF INNATE IMMUNITY AND TISSUE REPAIR

Although the primary focus of this review is murine and human studies, work in invertebrate animals reveal the ancient and critical role of neurons in immune responses (Figure 5). In primitive organisms that lack specialized immune cells, the nervous system is ideally equipped to carry out the functions of innate immunity. In *Caenorhabditis elegans* (*C. elegans*), sensory neurons such as ASI and ASH integrate external cues and coordinate protective host defense responses.[127] ASI neurons mediate pathogen avoidance behaviors, and *C. elegans* deficient in ASI sensory neurons exhibit enhanced susceptibility to the bacterial pathogen *P. aeruginosa*. In contrast, *C. elegans* deficient in ASH nociceptor neurons, which downregulate immune-related gene expression, had increased resistance to *P. aeruginosa* infection.[127] These observations contrast with the findings of an earlier study showing that ASI and ASH neurons both mediated immunosuppressive responses.[128] These neurons express OCTR-1, a G-protein-coupled catecholamine receptor, and loss of *octr-1* resulted in enhanced resistance to *P. aeruginosa*. Signaling through OCTR-1 resulted in the inhibition of the

unfolded protein response (UPR) by ASH and ASI neurons, which is essential for innate immunity in *C. elegans*.[128] NPR-1, another GPCR expressed by sensory neurons, was found to suppress innate immunity in *C. elegans*. *C. elegans* that were deficient in this NPR-1, which is related to the mammalian neuropeptide Y receptor, exhibited enhanced resistance to *P. aeruginosa*.[129] *C. elegans* neurons were also shown to impact immunity through secreted neuropeptides. In response to *Staphylococcus aureus* infection, neurons released Ach, which activated mAchR on intestinal epithelial cells. mAChR activation led to a WNT signaling cascade that resulted in the increased expression of immunity genes[130] (Figure 5A). These findings show that despite its structural simplicity (containing only 302 neurons), the *C. elegans* nervous system is functionally complex and critical for innate immunity in these invertebrates.

Recent work studying *Drosophila melanogaster* (*D. melanogaster*) has revealed another example of the ancestral peripheral nervous system acting as an effector of innate immunity in the gut. Following DSS- and bleomycin-mediated injury in the gut of *D. melanogaster*, TNF/Egr-sensing cholinergic neurons were shown to mediate tissue repair and the transition to homeostasis.[131] Knockdown of nAchR increased inflammation and cell death while delaying recovery in both DSS- and bleomycin-mediated gut injury. In contrast, overexpression of nAchRs resulted in expedited recovery and reduced inflammatory cytokines in the gut. Ultimately, a subset of anti-inflammatory recovery-regulating cholinergic enteric neurons (ARCENS) were identified as the primary producers of Ach in this pathway. These ARCENS responded to local inflammation by releasing Ach, which drove calcium flux to spread across the epithelium via gap junctions and promoted cell maturation and the transition to homeostasis (Figure 5B). These and other studies demonstrate that neuronal sensing of pathogens and neuronal regulation of inflammation during injury and homeostasis are evolutionarily ancient innate immune mechanisms.

CONCLUDING REMARKS

In this review, we have presented recent studies that reveal well-characterized mechanisms by which the nervous system regulates inflammation and homeostasis. The nervous system drives inflammation; host defense; and disease via local, systemic, and central mechanisms. At barrier tissues, these effects are mediated by crosstalk between sensory neurons, immune cell networks, epithelial tissues, and both commensal and pathogenic microbes. Many different immune cell types, including monocytes, macrophages, neutrophils, and T cells, express receptors for neuropeptides such as CGRP and SP. Upon activation by either exogenous or endogenous signals of infection or tissue damage, sensory neurons can directly modulate inflammation through local release of neuropeptides. While neuronal regulation of immunity is critical for limiting excess inflammation and promoting tissue homeostasis, microbial pathogens have evolved mechanisms to exploit neuroimmune signaling to enhance disease. Continued research to identify signals that activate neurons and to define neuronal effector functions could yield important insights into how sensory neurons can be targeted to treat diverse illnesses including infections, allergies, and other inflammatory conditions.

We have also raised a few questions provoked by our current understanding of these neuroimmune pathways and will conclude this review by offering some broad questions that we hope you may be able to apply to your research to further augment our understanding of neuroimmunity. (1) What tissue-specific mechanisms regulate neuroimmune pathways to determine their effector functions? Consistent with the concept of compartmentalized neuroimmune function,[132] (2) what tissue-specific effects do neuropeptides have on local stromal, epithelial, and endothelial cells during the models of innate immunity discussed in this review? Appreciating that many immune and non-immune cells can sense a variety of neuropeptides such as CGRP and SP, (3) how do immune cells translate multiple signals from the nervous system into discrete and specific effector functions? Recalling the ability of Th17 cells to drive neuronal regeneration, (4) what phenotypic changes are imposed on peripheral neurons during inflammation, and how may these changes impact homeostasis? Finally, reflecting on the example that immunologic memory can be stored in the insular cortex after DSS colitis,[133] (5) what changes occur to the CNS during host defense/disease, and how do these adaptations impact the host response to future insults and infections? We look forward to better understanding the answers to these questions and many others as the study of neuroimmunology continues to evolve.

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DECLARATION OF INTERESTS

I.M.C. serves on the scientific advisory boards of GSK Pharmaceuticals and Nilo Pharmaceuticals. D.H.K. serves on advisory boards for Janssen Pharmaceuticals and Galderma.

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