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Abbreviations

AD	Atopic dermatitis
AR	Allergic rhinitis
BDNF	Brain-derived neurotrophic factor
CGRP	Calcitonin gene-related peptide
CLR	Calcitonin receptor-like receptor
CNS	Central nervous system
DC	Dendritic cell
DRG	Dorsal root ganglia
EoE	Eosinophilic esophagitis
ERK	Extracellular signal-regulated kinase
FcεRI	High affinity IgE receptor
GFRα3	GDNF family receptor α3
GPCR	G protein-coupled receptor
H ₁	Histamine type 1 receptor
H ₂	Histamine type 2 receptor
H ₃	Histamine type 3 receptor
H ₄	Histamine type 4 receptor
IgE	Immunoglobulin E
IL	Interleukin
IL-31RA	IL-31 receptor A
IL-33R	IL-33 receptor
IL-4Rα	IL-4 receptor α
IL-5R	IL-5 receptor
ILC2	Group 2 innate lymphoid cell
JAK	Janus kinase
mAB	Monoclonal antibody
Mrgpr	

	Mas-related G protein-coupled receptor
NGF	Nerve growth factor
NK-1R	Neurokinin-1 receptor
NMU	Neuromedin U
NMUR1	NMU Receptor 1
OSMR	Oncostatin M receptor
p75 ^{NTR}	p75 neurotrophin receptor
PAR	Protease-activated receptor
PLC	Phospholipase C
RAMP	Receptor activity modifying protein
RCP	Receptor component protein
Sema3A	Semaphorin 3A
SP	Substance P
STAT	Signal transducer and activator of transcription
T _H 2	T helper type 2
Trk	Tropomyosin receptor kinase
TRP	Transient receptor potential
TRPA1	Transient receptor potential ankyrin 1
TRPV1	Transient receptor potential vanilloid 1
TSLP	Thymic stromal lymphopoietin
TSLPR	TSLP receptor
VIP	Vasoactive intestinal peptide
VIPR	VIP receptor

Abstract

A striking feature underlying all atopic disorders such as asthma, atopic dermatitis, and food allergy is the presence of pathologic sensory responses, reflexes, and behaviors. These symptoms, exemplified by chronic airway irritation and cough, chronic itch and scratching, as well as gastrointestinal discomfort and dysfunction, are often cited as the most debilitating aspects of atopic disorders. Emerging studies have highlighted how the immune system shapes the scope and intensity of sensory responses by directly modulating the sensory nervous system. Additionally, factors produced by neurons have demonstrated novel functions in propagating atopic inflammation at barrier surfaces. In this review, we highlight new studies that have changed our understanding of atopy through advances in characterizing the reciprocal interactions between the immune and sensory nervous systems.

Introduction

The term atopy refers to the genetic predisposition of patients to develop allergic disorders which most frequently affect epithelial barrier surfaces including the digestive tract, eyes, respiratory tract, and skin. These disorders include, but are not limited to, allergic rhinitis (AR), asthma, atopic dermatitis (AD), eosinophilic esophagitis (EoE), and food allergy. Atopic disorders have a profoundly negative impact on quality of life, and epidemiological evidence suggests that up to 30% of individuals worldwide will develop at least one of these disorders over their lifetime [1]. Additionally, early development of one allergic disorder predisposes individuals to the development of subsequent additional allergic disorders, a phenomenon referred to as the atopic march [2]. Thus, given their enormous public health burden, understanding the molecular and cellular bases of atopic disorders has emerged as a highly impactful area of investigation.

Allergic disorders, a subset of atopic hypersensitivities, are characterized by enhanced production of immunoglobulin E (IgE) and an allergic inflammatory profile including mast cell activation and eosinophil recruitment. Additionally, a striking, but poorly understood, feature

common to all allergic and atopic disorders is the presence of dysregulated sensory responses and resultant pathologic reflexes. These symptoms, exemplified by chronic itch and scratching in AD, airway irritation, bronchoconstriction, and cough in asthma, gastrointestinal discomfort and dysfunction in EoE and food allergy, and recurrent sneezing in AR, are frequently cited as the most debilitating aspects of these disorders. Importantly, damage to barrier surfaces due to these reflexes, such as skin barrier disruption caused by incessant scratching in AD, can result in exacerbated immune responses and contribute to the chronicity of atopic disorders [3]. Consequently, how the atopic immune response and dysregulated neuronal physiology interact to promote disease is a subject of intense exploration. In this review, we highlight recent studies unveiling novel neuroimmunologic pathways that regulate both inflammation and sensory responses in context of atopic inflammation.

Immune dysregulation in atopy

Although the etiology of atopy remains mysterious, several key discoveries have determined the common factors that drive atopic inflammation across multiple barrier surfaces. The identification of the predominantly epithelial cell-derived cytokines interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin (TSLP) unveiled a powerful mechanism by which the epithelium directly activates the immune system at barriers such as the gut, lung, and skin [4–10] (**Fig. 1**). In addition to acting directly on adaptive T helper type 2 (T_H2) cells, these molecules are potent activators of many innate immune cell populations including basophils, eosinophils, mast cells, and group 2 innate lymphoid cells (ILC2s) (**Fig. 1**). Collectively, this diverse population of immune cells promotes the production of the type 2 effector cytokines IL-4, IL-5, and IL-13, which in turn drive epithelial hyperplasia, mucous secretion, as well as the recruitment and activation of additional inflammatory cells at barrier surfaces (**Fig. 1**) [10–13].

Type 2 cytokines also act on B cells to promote immunoglobulin class-switching to generate IgE [11–13]. The resulting IgE can then bind mast cells and basophils via the high affinity IgE receptor FcεRI (**Fig. 1**). Engagement of IgE with environmental or food antigens results in crosslinking of FcεRI and rapid activation of mast cells and basophils. These granulocytes then release multiple small molecules and proteins including histamine, proteases, and inflammatory cytokines [12,14]. Although these factors have various proinflammatory functions, they have now been shown to have direct effects on the sensory nervous system. Given the highly debilitating nature of pathologic sensations and reflexes driven by neuroimmune interactions, a clearer understanding of how the immune and nervous systems shape one another is critical for the development of new therapeutics for atopic disorders.

Effects of the immune system on the sensory nervous system

The sensory nervous system is tasked with relaying peripheral signals to the brain. It broadly includes the somatosensory nervous system which transmits conscious perception of multiple sensations such as itch, nociception, mechanoreception, and proprioception through unique families of sensory neurons as well as the autonomic nervous system which transmits visceral sensations and homeostatic signals [15–18]. To accomplish this, sensory neurons send projections from their cell bodies, located in discrete ganglia throughout the body, toward both the central nervous system (CNS) and barrier surfaces. For example, conscious sensations from the skin of the body are carried along projecting axons of sensory nerves to the dorsal root ganglia (DRG) where their signals are then transmitted to the spinal cord and brain. Initiation of these signals begins in peripheral terminals of sensory neurons with localized depolarization due to activation of neuronal receptors and membrane ion channels. Given a sufficient stimulus, local activation can lead to increased action potential firing of projecting sensory neurons which results in CNS transmission. Thus, determining the function of specific receptors and channels expressed by sensory neurons at barrier surfaces is critical to understanding the mechanisms underlying dysregulated sensory responses.

While the activation of the sensory nervous system can ultimately involve many different ion channels, a family of membrane-bound proteins known as the transient receptor potential (TRP) channels frequently acts as a final common pathway for many different immune cell-derived stimuli. This group of proteins encompasses more than two dozen different channels and thus regulates a wide variety of sensory responses including itch, nociception, and thermoreception [18,19]. However, in the context of dysregulated sensory responses in atopy, TRP ankyrin 1 (TRPA1) and TRP vanilloid 1 (TRPV1) are the most commonly studied due to their critical roles in mediating sensory responses to atopic stimuli (**Fig. 2**). Broadly, activation of a variety of receptors expressed on the peripheral terminals of sensory nerve fibers results in the engagement and activation of various TRP channels. These channels then depolarize sensory neurons via entry of cations to reach the firing threshold of voltage-gated sodium channels, resulting in transmission of peripheral signals to the CNS [16,18]. Given our understanding of the initiation of these neuronal responses, recent work has begun to focus on factors elevated in atopic inflammation as well as associated receptors in the sensory nervous system that control these signaling events.

Canonical responses: Histamine

One of the earliest described and well-defined examples of atopic inflammation-associated stimuli activating the sensory nervous system is neuronal activation by histamine. Following activation of mast cells and basophils by engagement of IgE on FcεRI, histamine is released and binds its receptors on sensory neurons such as the histamine type 1 receptor (H₁) [20–23]. H₁ is a G protein-coupled receptor (GPCR), and activation of H₁ results in signaling through G_q and phospholipase C (PLC) to activate TRP channels, especially TRPA1 and TRPV1 (**Fig. 2A**) [20–23]. However, despite its early identification and characterization, antagonism of H₁ alone typically does not yield clinically meaningful therapeutic outcomes for treating neuronal processes underlying atopic disorders such as a chronic itch associated with AD [24].

Since the initial discovery of H₁, additional members of the histamine receptor family have been described. These include H₂ expressed most highly in the stomach, H₃ expressed in the immune system and CNS, and H₄ found on immune cells as well as DRG sensory neurons [23,25,26]. Strikingly, even though antagonism of H₁ has historically demonstrated limited efficacy in treating atopic disorders, new clinical trials using novel antagonists to H₄ are more promising, indicating that this pathway may play a role in atopy [27,28]. Collectively, the persistence of pathologic sensory responses in atopy despite traditional anti-histamine treatment suggests the existence of histamine-independent means of neuronal activation, and intense interest has turned to identifying these pathways and determining their importance in atopy.

New frontiers in atopy: Histamine-independent neuronal activation

In addition to histamine, granulocytes including mast cells and basophils can release the protease tryptase during inflammation [12,14]. Indeed, elevated levels of tryptase can be found in some patients with atopic disorders, especially after acute allergen exposure [12,14,29]. Tryptase is known to activate sensory neurons via a family of specialized GPCR proteins named protease-activated receptors (PARs) (**Fig. 2A**). In particular, PAR2 is expressed by sensory neurons and contains an extracellular tail that, when cleaved by tryptase or other proteases, can bind the signaling domain of the receptor to activate further downstream signaling pathways including TRP channels to result in sensations like itch (**Fig. 2A**) [29]. Although PAR2 expression by sensory neurons in the skin is responsible for at least some of the itch effects of proteases in the skin, the contribution of neuronal PAR2 signaling at other barrier surfaces is less well explored.

In addition to PAR2 signaling, a family of receptors expressed by sensory neurons known as the Mas-related G protein-coupled receptors (Mrgprs) is now known to play a key role in histamine-independent activation of sensory neurons (**Fig. 2A**) [30]. The Mrgpr family represents about 50 genes in mice and at least 4 genes in humans [31–33], suggesting a

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broad ability of this group of proteins to sense multiple ligands. Although the Mrgpr family was originally identified to mediate itch via a small population of sensory neurons that innervates the skin, these receptors are also expressed on sensory neurons that innervate other barrier surfaces including the lung [33]. Thus, the Mrgpr family likely plays a unique role in a variety of tissues to mediate multiple physiologic processes and has emerged as an exciting area of inquiry. However, unlike PAR2, the endogenous ligands for members of the Mrgpr family are not yet clearly defined. Collectively, these new studies demonstrate that histamine-independent sensory pathways may contribute significantly to atopic disorders. However, future clinical trials with agents that disrupt these pathways will be required to fully determine the importance of these pathways in humans with atopy.

Cytokine regulation of sensory responses

Because cytokines play such a critical role in the pathogenesis of atopic disorders, it was hypothesized that these signaling molecules may also directly influence sensory neurons. The discovery of the IL-31 receptor on a small subpopulation of sensory neurons established IL-31 as the first type 2 inflammation-associated cytokine that directly activates the sensory nervous system [34–37] (**Fig. 2A**). Unlike histamine, which is derived primarily from granulocytes, IL-31 is believed to be released from activated T_H2 cells in both mice and humans [34–37], indicating multiple cells of the immune system can shape sensory responses in atopy. Strikingly, both intradermal and intrathecal injections of IL-31 into mice lead to robust scratching responses [34]. Similar to histamine, direct activation of sensory neurons by IL-31 depends on TRP channels, namely TRPA1 and TRPV1 (**Fig. 2A**) [35]. However, while activation of neurons by histamine depends on G_q signaling, the receptor for IL-31, a heterodimeric protein composed of IL-31 receptor A (IL-31RA) and oncostatin M receptor (OSMR), activates other intracellular pathways such as ERK signaling [35]. Thus, how activation of the IL-31 receptor results in the activation or modification of TRP channels remains to be fully defined and is an active area of investigation. Additionally, new studies have begun to explore if other cytokines have similar neuromodulatory properties in atopy.

Although direct activation and robust depolarization of sensory neurons by molecules like histamine and IL-31 play important roles in atopic disorders, recent studies have demonstrated that chronic inflammation can also change baseline neuronal physiology such as increasing neuronal sensitivity. This is exemplified by enhanced sensitivity to pruritogens, a term for substances that elicit sensations of itch, in AD [38–40] and increased sensitivity to cough-inducing stimuli in asthmatics [41]. Thus, studies examining the effects of atopic inflammation on the nervous system have expanded to include studying pathways that durably modify neuronal physiology beyond triggering action potential firing or acute behavioral responses alone. For example, a recent study identified that IL-5 activates sensory nerve fibers in the setting of asthma [42] (**Fig. 2A**). However, in contrast to histamine or IL-31, *in vitro* stimulation of sensory neurons that innervate the lung with IL-5 led to activation as measured by calcium influx but not spontaneous action potential firing [42]. Extending these findings, we identified that the type 2 cytokines IL-4 and IL-13 directly stimulate mouse and human sensory neurons that innervate the skin as determined by calcium influx [43] (**Fig. 2A**). Single-cell RNA-sequencing of DRG neurons revealed preferential expression of IL-4 receptor α (IL-4R α), the shared receptor subunit for IL-4 and IL-13, on multiple predicted itch-sensory neurons such as those that express IL-31RA and Mrgpr proteins compared to other sensory modalities like pain or mechanoreception [17,43]. Surprisingly, unlike other pruritogens like histamine and IL-31, intradermal injection of IL-4 and IL-13 *in vivo* did not elicit acute itch responses [43]. However, conditional deletion of IL-4R α in sensory neurons resulted in marked abatement of chronic itch in an experimental model of AD [43]. Further investigation of this phenomenon revealed that IL-4R α signaling sensitized sensory neurons to a number of other pruritogens present in AD lesions. Thus, neuronal stimulation by type 2 cytokines represents an important and novel paradigm of neuroimmune crosstalk that can be initiated by both the innate and adaptive immune systems. Further, these studies suggest that cytokines may have unique effects beyond classical activation that extend to the immune system tuning neuronal physiology.

The intracellular signaling pathways that facilitate the neuronal effects of cytokines are largely unknown and now being investigated. As in lymphocytes, we have found that cytokine signaling in sensory neurons is dependent on the Janus kinase (JAK) pathway. Specifically, IL-4-mediated activation of sensory neurons is dependent on downstream JAK1 [43] (**Fig. 2A**). Neuronal JAK1 signaling may lead to STAT-mediated transcriptional changes that result in cellular activation as is classically described in immune cells. However, we speculate that JAK1 may have novel targets in neurons given the rapidity of neuronal responses to cytokines. These targets may include TRP channels as previous studies have demonstrated these proteins can be phosphorylated to modulate neuronal activity [19,44–46]. Strikingly, recent studies in both mice and humans have identified activating mutations in JAK1 that result in pruritic dermatoses [47–49]. Bone marrow transplantation with wild-type bone marrow into mutant JAK1 mice as well as potent systemic immunosuppression in patients with activated mutant JAK1 did not resolve the aberrant inflammation and chronic itch. Thus, activated JAK1 may be driving sensory responses through direct modification of non-hematopoietic cells, including sensory neurons. Notably, targeted therapy using JAK inhibitors have been shown to improve itch sensations in patients with JAK1 activation mutations as well as patients with AD [49,50]. However, the intracellular mechanisms by which type 2 cytokine signaling promotes neuronal activity as well as their clinical relevance remain to be fully determined.

Upstream contributions of epithelial cells

The epithelial cell-derived cytokines IL-25, IL-33, and TSLP are master initiators of type 2 inflammation at barrier surfaces and induce the production of type 2 effector cytokines (**Fig. 1**). However, TSLP is also known to directly activate neuronal TSLP receptor (TSLPR) and mediate itch in mice through activation of PLC and TRPA1 [51] (**Fig. 2B**). From this study, a new paradigm emerged in which the damaged epithelial barrier, in addition to initiating a rapid type 2 cytokine response, can also stimulate the sensory nervous system. Similarly, other studies have identified that the epithelial cell-derived alarmin IL-33 and chemokine

CXCL10 can also activate sensory neurons through neuronal IL-33 receptor (IL-33R) and CXCR3, respectively, and contribute to itch in models of allergic contact dermatitis [52,53] (**Fig. 2B**). However, the relative contributions of cytokine signals from the epithelium compared to cytokines from the immune system in the context of itch and other sensory responses remain to be fully defined. Further, we speculate that cytokines such as TSLP and IL-33 may have dual functions as danger signals via direct epithelial-neuronal axes as well as indirectly via intermediate immune cell populations. How the sensory nervous system integrates these different signals from both epithelial and immune cells remains an essential question in sensory biology.

Hyperinnervation in atopy

Histological analyses of tissues from atopic patients have revealed striking increases in innervation at sites of inflammation. This was identified early in the skin of patients with AD [54,55] but has now been shown in other tissues such as the lung in asthma [56]. This increase in sensory neuron density is believed to contribute to atopic hypersensitivity, and worsening barrier damage, potentially caused by chronic itching or coughing, has been shown to increase tissue innervation [57]. These observations support a pathogenic cycle of inflammation and behavioral responses that promotes neuron outgrowth which, in turn, worsens atopic disorders.

Experimental systems have begun to define the factors that drive hyperinnervation at barrier surfaces. One such factor upregulated in the skin of AD patients is nerve growth factor (NGF) [55], with additional studies describing increased NGF levels in asthma [58,59]. Although NGF can promote the upregulation of receptors and control transcriptional activation to increase neuronal sensitivity, it is primarily a driver of neuron growth through the receptor TrkA and to a lesser extent p75^{NTR} [60] (**Fig. 2C**). Epithelial cells like keratinocytes make NGF, along with immune cells such as eosinophils, mast cells, and Langerhans cells [60,61]. Other members of the NGF-family of neurotrophins, including brain-derived

neurotrophic factor (BDNF) which binds the receptor TrkB, are similarly upregulated in atopic inflammation [62,63] and also exert pro-growth effects on peripheral neurons (**Fig. 2C**). Thus, the study of NGF and other neurotrophins has allowed for a better understanding of how chronic inflammation can direct pathologic neuronal outgrowth at epithelial barrier surfaces.

Since the identification of the role of the NGF family in atopic inflammation, additional neurotrophic factors have been implicated in atopic disorders including artemin, which binds its receptor composed of the RET tyrosine kinase and the GFR α 3 co-receptor, and IL-31 [64–66] (**Fig. 2C**). Interestingly, these observations may help explain the influence of environmental pollution on atopy as exposure of mice to common pollutants resulted in elevated artemin signaling and hyperinnervation in the skin [64]. Recently, IL-31 was also shown to specifically promote the growth of small diameter neurons implicated in itch [65]. Although scratching responses due to IL-31-mediated activation of sensory neurons is known to be dependent on TRPV1, the effects on neuronal growth of IL-31 signaling were observed to be independent of TRPV1 [65]. Collectively, these studies have started to uncover the diversity of factors and signaling pathways derived from both the epithelial barrier and immune system that result in tissue hyperinnervation.

In parallel with the upregulation of factors that promote tissue innervation in atopy, factors that limit neuron growth may be lost in inflammation. These factors include Semaphorin 3A (Sema3A), a protein that regulates neuronal axon growth, that is downregulated in lesional AD skin [67], while treatment of AD lesions reduces skin hyperinnervation and is associated with increased Sema3A levels [68–70]. However, the factors that control the balance of neuronal growth and repulsive factors as well as whether these factors control innervation at other barrier surfaces are not known. Ultimately, these studies highlight multiple effects of the immune system on the sensory nervous system that range from local activation and

regulation of neuronal sensitivity to tissue level changes including alteration in barrier innervation patterns.

The role of the sensory nervous system in modulating atopic inflammation

Activation of the sensory nervous system has been widely observed to influence inflammatory processes over the last century [71]. Thus, in addition to afferent effects on the nervous system by the immune system, sensory neurons can clearly modulate immune responses in an efferent manner. Further, clinical cases have demonstrated improvements in inflammatory skin disorders after injury to nerves projecting to skin lesions [72–74], suggesting a critical role for the nervous system in propagating barrier inflammation.

Neuronal activation of the immune system

The peripheral projections of sensory neurons are classically categorized as originating from neurons that have a high capacity to release proteins (peptidergic) and those that release much less of these factors at barrier surfaces (non-peptidergic) [15,16]. These proteins are typically small peptides such as tachykinins like Substance P (SP), as well as calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), and neuromedin U (NMU) (**Fig. 3**). New studies have demonstrated how these factors can have profound influences on the immune system and exploring their roles in atopy has emerged as a key area of mucosal immunology.

SP is one of the earliest identified factors from the nervous system that exerts a powerful proinflammatory effect on the immune system. Activation of mast cells by SP can lead to degranulation and release of inflammatory mediators [75–77], while increasing the survival and proliferation of eosinophils [78] and T cells [79] (**Fig. 3**). SP primarily activates the neurokinin-1 receptor (NK-1R), although other members of the neurokinin receptor family can be weakly activated by SP [76]. As expected, given the broad proinflammatory properties of SP, many immune cells express NK-1R such as T and B cells [79,80],

monocyte and macrophages [81], dendritic cells (DCs) [82], eosinophils [78], and mast cells [77,83,84] as well as stromal cells like keratinocytes [85,86] and smooth muscle cells [87] (**Fig. 3**). Interestingly, IL-4 has also been shown induce the upregulation of the SP receptor on mast cells, indicating that SP may work to amplify allergic responses [88]. However, clinical trials for NK-1R antagonists alone have demonstrated mixed efficacy in atopic disorders [89]. The identification of the Mrgpr family of receptors, especially MrgprB2 in mice and MrgprX2 in humans on mast cells (**Fig. 3**), may explain these negative outcomes as SP has been shown to mediate mast cell release of proinflammatory factors through these receptors [77,83,84]. Thus, determining optimal approaches for manipulating SP signaling is an exciting therapeutic strategy in disrupting neuronal contributions to type 2 inflammation.

Sensory neurons that produce SP often also produce CGRP, another neuropeptide that is upregulated in atopic disorders [90–92]. This neuropeptide binds receptors composed of a calcitonin receptor-like receptor (CLR) subunit paired with one of three members of the receptor activity modifying protein (RAMP) family members [93]. The high affinity CGRP receptor, a complex of CLR, RAMP1, and an additional protein called receptor component protein (RCP), is found in many immune cell subsets and blood vessels [93]. In the context of atopy, CGRP plays an important role in augmenting type 2 immune responses (**Fig. 3**). For example, T cells cultured with DCs that had been previously exposed to CGRP produced more IL-4 and type 2 inflammation-associated chemokines like CCL17 and CCL22 compared to T cells cultured with naïve DCs [94]. Likewise, mice deficient in CGRP signaling have impaired type 2 immunity in an allergen-driven model of asthma [95]. Similar observations have been made in human mast cells from asthmatics, which released more histamine compared to healthy controls when incubated with CGRP [96]. In the setting of AD, T cells from AD patients produced more IL-13 compared to controls in response to CGRP [97]. However, another study has shown that CGRP treatment can impair the ability of DCs to induce eosinophilic airway inflammation [98]. Thus, more studies are warranted to better understand how CGRP modulates the immune system in various disease contexts.

Recent studies have identified novel neuroimmune interactions between the nervous system and ILC2s in both the gut and lung. In these contexts, both sensory neuron-derived VIP [42,99] and NMU [100–102] have emerged as potent activators of ILC2s. Although described earlier to drive T_H2 cell activation and T cell stimulation by DCs [103–105], ILC2s also express high levels of the VIP receptors VIPR1 and VIPR2 [42,99], and VIP has now been shown to aggravate experimental asthma by increasing IL-5 and IL-13 production by ILC2s [42,99] (**Fig. 3**). Similarly, NMU has also been shown to potently induce production of IL-5 and IL-13 in the gut [100,101] and lung [102]. Strikingly, one member of the NMU receptor family, NMUR1 is expressed specifically on ILC2s compared to other innate and adaptive immune cells, and stimulation of ILC2s with NMU led to increased IL-5 and IL-13 production compared to known cytokine activators of ILC2s [100–102] (**Fig. 3**). Thus, VIP and NMU released from neurons may jumpstart type 2 inflammation by acting on innate immune cells that are then further activated by other subsequent signals. Collectively, these studies demonstrate that the sensory nervous system has a direct role in shaping type 2 immune responses through both adaptive and innate immune cells at multiple barrier surfaces.

Neuronal regulation of cellular motility

In addition to directly activating the immune system, the sensory nervous system can regulate the motility of immune cells at barrier surfaces. Factors like SP and CGRP can broadly promote immune cell recruitment by acting on smooth muscle and endothelial cells to alter vascular tone and permeability [76,106] (**Fig. 3**). For example, SP can induce expression of endothelial cell adhesion molecules to rapidly recruit granulocytes like neutrophils and eosinophils [107]. More recently, selective interactions have been observed between neurons and multiple immune cell populations including mast cells [60,108,109], eosinophils [110], macrophages and DCs [111–114], T cells [100,101], and ILC2s [100,101] (**Fig. 3**). Collectively, these findings suggest that specific neuron-derived factors may direct specialized cellular immune responses at mucosal surfaces. Identifying the unique molecular

signals that dictate such neuroimmune processes has emerged as an exciting approach to better understand the pathogenesis of atopic disorders.

Perspectives

In contrast to other host-protective mechanisms, type 2 immunity evolved to combat helminth parasites that penetrate epithelial barrier surfaces. Although the epithelium functions as a physical barrier, the discovery of epithelial cell-derived cytokines has uncovered how the barrier can function as an immune organ. In addition to the immune system, the mammalian host also employs sensory responses to evoke host-protective behavior such as coughing and scratching to mechanically remove noxious stimuli. Recent studies have now described a novel neuroimmunologic paradigm in which inflammatory factors such as cytokines can directly influence such sensory responses and behaviors. Further, sensory neurons themselves can in turn direct immune responses at mucosal barrier surfaces. Thus, incorporating recent discoveries characterizing these neuroimmune interactions has become essential to understanding pathogenesis of atopic disorders such as AR, asthma, AD, EoE, and food allergy.

Indeed, targeting neuroimmunologic processes has begun to emerge as a novel and potentially effective therapeutic strategy in atopic disorders. Dupilumab, a recently approved monoclonal antibody (mAb) against IL-4R α , has demonstrated unprecedented efficacy in the setting of AD [115–117]. Our recent studies have uncovered novel neuronal mechanisms by which modulation of IL-4R α signaling may have direct therapeutic implications in this context [43]. Similarly, nemolizumab, an anti-IL-31RA mAb has also emerged as a potential anti-itch agent in AD [36], presumably due to its effects on neuronal IL-31 signaling. Along these lines, Phase 2 or Phase 3 clinical trials are currently underway for anti-TSLP mAb, anti-IL-5 mAb, anti-IL-13 mAb, anti-IL-33 mAb treatments, as well as selective JAK inhibitors and antagonists for proinflammatory factors from the nervous system for many atopic disorders.

Whether these therapies will derive part of their efficacy from modulating neuroimmune processes remains an exciting area of translational and clinical research.

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Author contributions

L.K.O. and B.S.K. wrote the manuscript and designed the figures.

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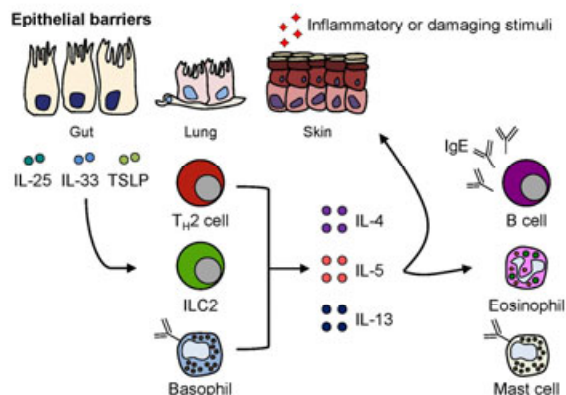


Figure 1. Atopic inflammation at epithelial barrier surfaces.

Inflammatory and damaging stimuli at epithelial barrier surfaces including the gut, lung, and skin result in the release of the epithelial cell-derived cytokines IL-25, IL-33, and TSLP. These cytokines potently activate type 2 cellular immune responses that define atopic inflammation via the production of the type 2 cytokines IL-4, IL-5, and IL-13. IgE, Immunoglobulin E; ILC2, Group 2 innate lymphoid cell; T_H2, T helper type 2; TSLP, Thymic stromal lymphopoietin.

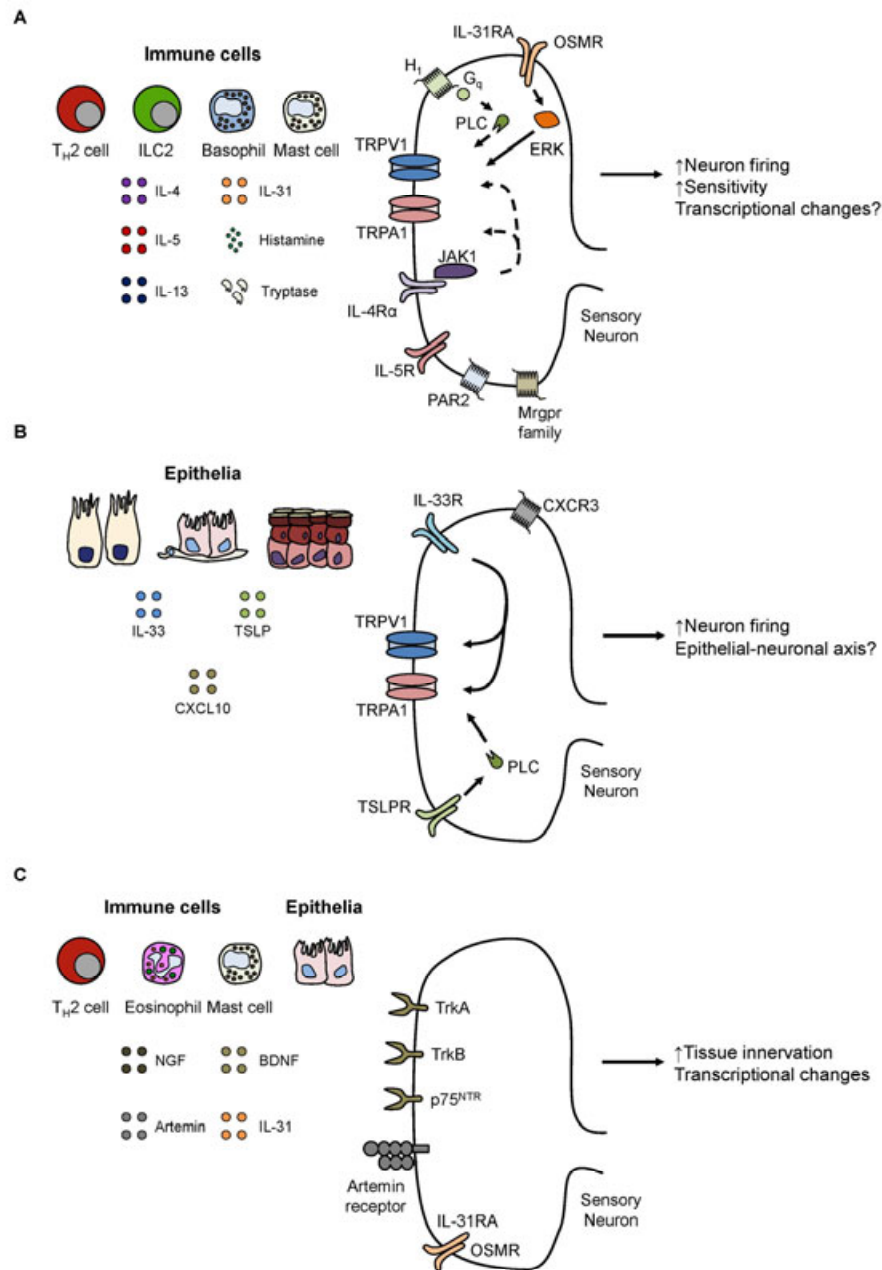


Figure 2. Immune and epithelial processes that regulate sensory responses.

Type 2 immune responses have profound effects on the sensory nervous system in the setting of atopy. **(A)** Small molecules like histamine and proteins like tryptase, as well as

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effector cytokines including IL-4, IL-5, IL-13, and IL-31 from the immune system can directly activate sensory neurons. Neuronal responses to cytokines are broadly dependent on the ion channels TRPA1 and/or TRPV1, although the intracellular pathways that result in TRP channel activation in this context remain to be fully defined. **(B)** Epithelial cell-derived cytokines such as IL-33 and TSLP and the chemokine CXCL10 can also promote pathologic sensory responses in the setting of atopy. **(C)** Additionally, the immune system and epithelia produce growth factors like NGF, BDNF, artemin, and IL-31 which promote hyperinnervation at barrier surfaces. BDNF, brain-derived neurotrophic factor; ERK, extracellular signal-regulated kinase; H₁, Histamine type 1 receptor; IL-4R α , IL-4 receptor α ; IL-5R, IL-5 receptor; IL-31RA, IL-31 receptor A; IL-33R, IL-33 receptor; ILC2, Group 2 innate lymphoid cell; Mrgpr, Mas-related G protein-coupled receptor; NGF, Nerve growth factor; OSMR, Oncostatin M receptor; p75^{NTR}, p75 neurotrophin receptor; PAR2, Protease-activated receptor 2; PLC, Phospholipase C; T_H2, T helper type 2; Trk, Tropomyosin receptor kinase; TRPA1, Transient receptor potential ankyrin 1; TRPV1, Transient receptor potential vanilloid 1; TSLP, Thymic stromal lymphopoietin; TSLPR, TSLP receptor.

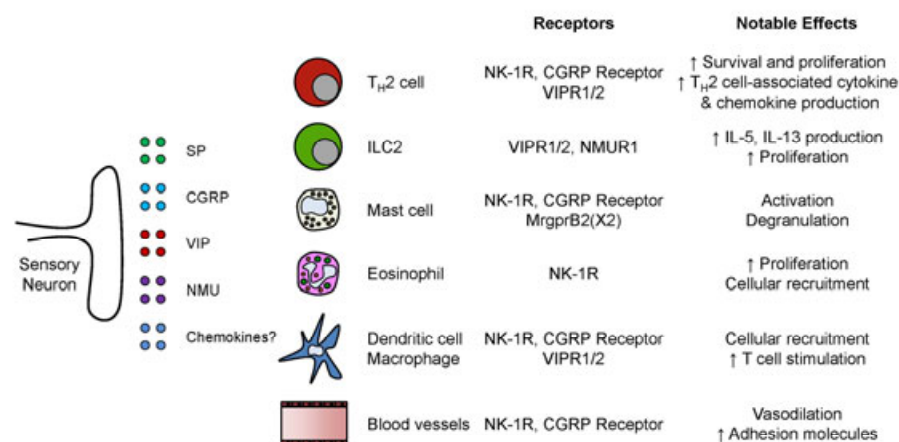


Figure 3. Sensory neurons influence mucosal immune responses.

The nervous system can release multiple neuropeptides that broadly promote atopic inflammation including SP, CGRP, VIP, and NMU in mice and humans. These factors can synergistically augment type 2 immune responses such as increased production of type 2 cytokines and chemokines from T_H2 cells, increased cytokine production from ILC2s, activation of mast cells, macrophages and dendritic cells, as well as increased cellular proliferation in multiple cell types including T_H2 cell, ILC2s, and eosinophils. The sensory nervous system can also recruit inflammatory cells to barrier surfaces through vasodilation and increased expression of endothelial adhesion molecules. Additionally, many immune cells have specific, dynamic interactions with the sensory nervous system, but the chemokines or additional factors that mediate these interactions have yet to be fully identified. CGRP, Calcitonin gene-related peptide; ILC2, Group 2 innate lymphoid cell; NK-1R, Neurokinin-1 receptor; Mrgpr, Mas-related G protein-coupled receptor; NMU, Neuromedin U; NMUR1, NMU Receptor 1; SP, Substance P; T_H2, T helper type 2; VIP, Vasoactive intestinal peptide; VIPR, VIP Receptor.