



Bidirectional sensory neuron–immune interactions: a new vision in the understanding of allergic inflammation

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Peripheral neurons (including sensory neurons) are ubiquitously distributed in all tissues, particularly at the interface with the environment. The primary function of sensory neurons is the transmission of sensations of temperature, pain and itch to elicit appropriate behavioral responses. More recently, sensory neurons have emerged as potent regulators of type 2 immune responses and allergic inflammation. There is increasing evidence showing that neurons can express receptors previously thought to be restricted to the immune compartment. In addition, certain subtypes of immune cells (e.g. mast cells, ILC2s or macrophages) also express specific neuroreceptors that provide them with the capacity to integrate neuron-derived signals and modulate their activation status during the development of allergic inflammation.

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Introduction

Nociception is the sensing of noxious chemical, mechanical, or thermal stimuli. First introduced by Sherrington in

1900 in the context of pain perception [1], nociception allows animals to rapidly sense and avoid environmental hazards including piercing objects, burning heat, and freezing temperatures [2]. The immune system provides an additional layer of protection in the event that prevention of invasion by pathogens is breached even with optimal sensing and behavioral avoidance of environmental threats. Allergy (i.e. hypersensitivity) is a pathologic inflammatory and, subsequent neurosensory, process that is triggered by exaggerated responses to otherwise harmless environmental substances.

The skin and mucous membranes of the respiratory and gastrointestinal tracts are highly innervated by primary sensory neurons, referred to broadly as nociceptors. These barrier surfaces are the first line of defense against environmental stimuli and also the most commonly affected by allergic diseases like eczema, asthma, and food allergy. Sensory and physiologic symptoms include itching, sneezing, coughing, and bowel dysmotility, which are closely linked to nociception. Emerging studies have unveiled how allergic inflammation and sensory neurons intersect at barrier surfaces to shape the host response. On the one hand, inflammatory molecules like cytokines derived from immune cells during allergy, or allergens themselves, may act on sensory neurons; on the other hand, nociceptors in turn release neuropeptides and shape barrier immunity [3[•],4[•],5[•]]. Herein, we highlight recent advances in our understanding of such bidirectional neuro-immune cross talk.

Unraveling the identity of sensory neurons

The cell bodies of nociceptors, or sensory neurons, are located in either the trigeminal ganglia, which innervate the head and neck, or the dorsal root ganglia (DRG) which receive signals from the rest of the body. These afferent neurons receive signals from the tissue and transmit impulses to the spinal cord, where information is relayed by projection neurons towards the brain and sensation is perceived [6]. Sensory neurons that are specialized to sense itch are referred to as pruriceptors. It is now well established that in addition to nociception, pruriception is yet another distinct sensory process at the molecular and cellular level [7,8].

Most nociceptors and pruriceptors are small diameter unmyelinated C fibers [9]. In development, C fiber neurons initially appear as one population characterized by

expression of the nerve growth factor receptor TrkA. However, later in development they diverge into two subpopulations, one that maintains TrkA expression, and the other that downregulates expression of TrkA [10] while upregulating the common glial-derived neurotrophic factor family ligand receptor Ret that is selectively labeled by isolectin B4 (IB4) [11]. TrkA-expressing nerve fibers also express neuropeptides like substance P (SP) and calcitonin-gene related peptide (CGRP), and are thus referred to as peptidergic (PEP) neurons. In contrast, IB4-positive nerve fibers generally do not express SP or CGRP during development period and are thus considered non-peptidergic (NP) [9,12,13*,14]. However, emerging studies using unbiased single-cell RNA sequencing (scRNA-seq) of murine DRG neurons have revealed that some NP neuron clusters also contain markers for PEP neurons (i.e. CGRP gene *Calca*) [15,16]. Therefore, it is likely that neurons traditionally considered NP have the capability of releasing neuropeptides as well. Thus, a major area of future inquiry will be in understanding the precise identity of individual neurons that are specialized to encode specific sensations, release distinct neuropeptides, or perform both functions to shape tissue immunity and inflammation.

Sensory neurons rely on specific sensors to detect different noxious stimuli such as the transient receptor potential (TRP) V1 and TRPA1 ion channels. TRPV1 is the receptor for capsaicin (the spicy ingredient of chili peppers) and also has the capacity to detect noxious heat [17,18]. TRPA1 (30% co-expressed with TRPV1 on somatosensory neurons) can be activated by different chemical compounds such as garlic (allicin) and mustard oils (allyl isothiocyanate) to cause pain [19]. Thus, in addition to specific receptors on sensory neurons mediating various sensations, the quality and intensity of such processes are modified by additional ion channels.

Neurons as sensors of immune stimuli

There is increasing recognition that nociception is modulated by the immune system. A variety of tissue-resident cells like mast cells (MCs) and macrophages/microglia

have been implicated in nociception via their production of cytokines and granule-associated mediators [20**,21**]. Meningeal mast cell and sensory neuron bi-directional interactions for instance, play fundamental roles in migraine pathophysiology, resulting in the sensitization of trigeminal nociceptors [22]. IL-1 β and TNF- α are two of the first cytokines shown to act directly on the nervous system in the context of pain [23–27]. Both IL-1 β and TNF- α -induced neuronal excitability is dependent on p38-MAPK downstream signaling and the activation of ion channels like TRPV1 [25,28,29]. Other cytokines such as IL-6 and IL-17A have also been identified to promote pain in joint inflammation models [30,31]. In contrast, the anti-inflammatory cytokine IL-10 has been shown to attenuate pain responses recently [32*]. Taken together, it appears that the sensory nervous system can both sense stimuli that promote noxious signals or even be modulated to suppress nociception. However, how such neuroimmune biology translates across the variety of sensory neurons innervating different organs remains a vibrant area of exploration [33*,34].

In addition, a number of cytokines that are upregulated in allergy have the capability to act on pruriceptors. In 2013, Wilson *et al.* found that, the epithelial cell-derived cytokine thymic stromal lymphopoietin (TSLP) promotes itch by stimulating itch-sensory neurons [35]. Later in 2014, IL-31 was shown to activate pruriceptors and thus, is the first type 2 immunity-associated cytokine to function as a pruritogen [36]. In 2017, Oetjen *et al.* identified that IL-4R α , the receptor for the canonical type 2 effector cytokines IL-4 and IL-13, is expressed by itch-sensory neurons and depend on downstream Janus kinase (JAK) signaling to promote neural hypersensitivity [37]. Indeed, blockade of TSLP, IL-31, IL-4R α , IL-13, and JAK are either approved or currently in clinical trials for the treatment of atopic dermatitis (AD) and/or other chronic itch disorders (Table 1) [38–50]. Collectively, these basic and translational advances illustrate how, in addition to external environmental stimuli, sensory neurons can respond to endogenous cytokine signals to elicit, enhance, and even suppress pain and itch in tissues.

Table 1

Innovated therapeutic approaches for atopic dermatitis

Target	Medication	Mode	Reference/NCT number
IL-31RA	Nemolizumab	mAb	[48–50]
TSLP	Tezepelumab	mAb	[46] NCT02525094; NCT03809663
IL-4R α	Dupilumab	mAb	[47,72–74]
IL-13	Tralokinumab	mAb	[41,42,45]
	Lebrikizumab		
JAK1, 2, 3	Baricitinib	Inhibitors	[38–40,43,44]
	Upadacitinib		
	Ruxolitinib cream		
	Delgocitinib ointment		

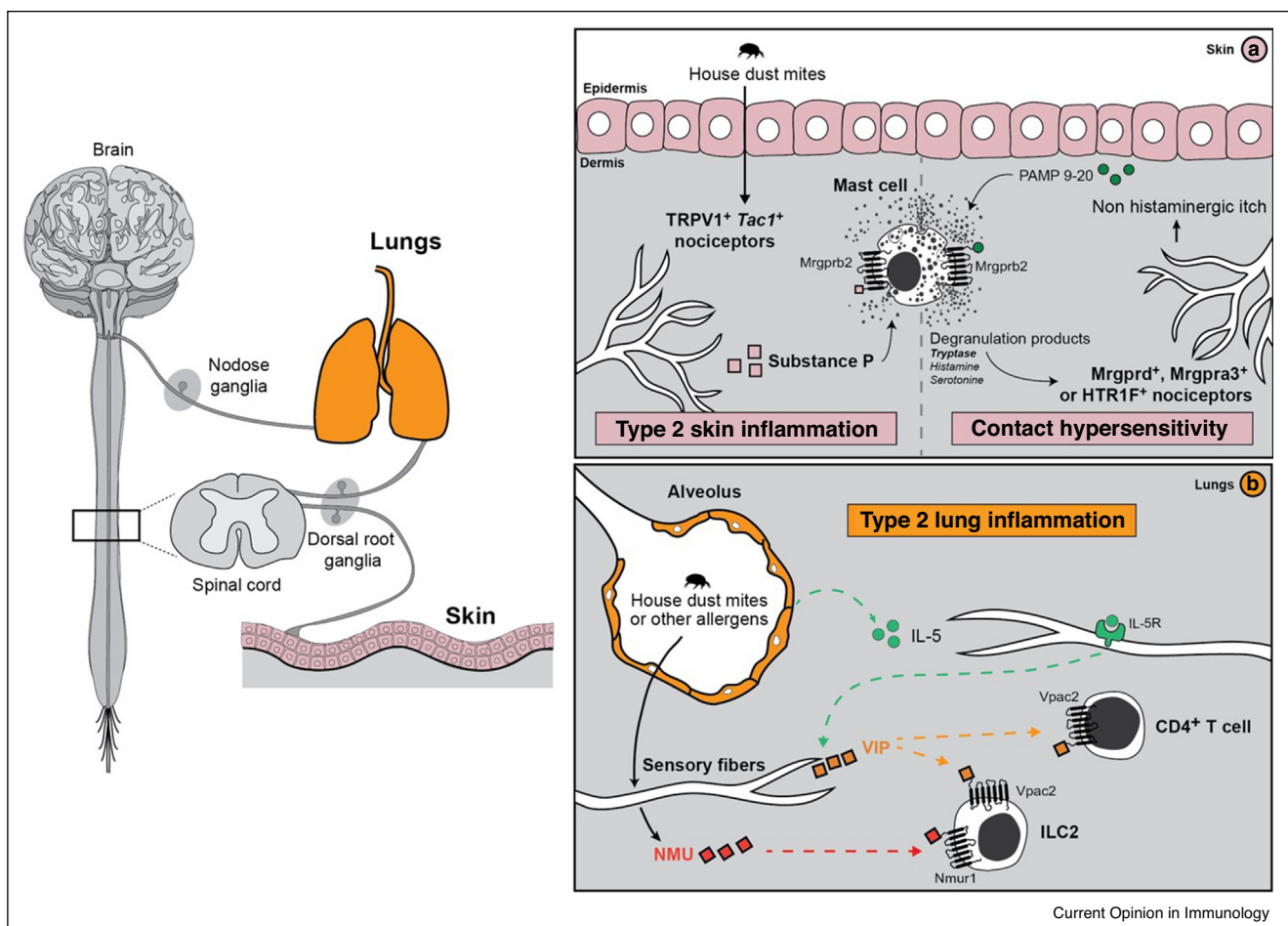
Abbreviations: JAK, Janus kinase; NCT, National Clinical Trial; mAb, monoclonal antibody; TSLP, thymic stromal lymphopoietin.

Role of sensory neurons in the regulation of allergic skin diseases

AD is a frequent chronic inflammatory skin disease with strong impact on health-related quality of life, especially due to itch burden [51[•]]. It was generally thought that pruriceptors were involved in manifestations of type 2 (allergic) skin diseases, such as AD, mainly by promoting itch-induced scratching behavior. Recently, a new role was uncovered by Basso *et al.* for SP-producing sensory neurons in regulating Mrgprb2⁺ MC activation and subsequent development of type 2 skin inflammation [52^{••}] (Figure 1a). The authors demonstrated that, compared with wild type (WT) mice, mice depleted in TRPV1⁺ sensory neurons, *Tac1*^{-/-} mice (that lack SP), MC-deficient mice and *Mrgprb2*^{-/-} mice, were protected from the

development of pathogenic type 2 inflammation and associated skin lesions. They then showed that common domestic allergens with cysteine protease activity, for example, house dust mites (HDMs), could directly activate TRPV1⁺ neurons to release SP. Using a new intravital imaging method, they showed that a large proportion of projections from activated TRPV1⁺ nociceptors formed physical contacts with MCs, and that penetration into the dermis of HDMs led to the sequential activation of nociceptors and adjacent MCs (Figure 1a). This study strongly suggests that TRPV1⁺ *Tac1*⁺ nociceptors and Mrgprb2⁺ MCs form 'sensory clusters' capable of detecting the presence of allergenic alarms and initiating the development of pathogenic type 2 immune responses in the skin [52^{••}]. Based on these results, it would be

Figure 1



Neuroimmune interactions play a crucial role in models of allergic skin and lungs disorders.

(a) Widely distributed domestic allergens can directly activate TRPV1⁺ *Tac1*⁺ nociceptor-Mrgprb2⁺ MC sensory clusters to drive the development of type 2 skin inflammation [52^{••}]. MC activation through the receptor Mrgprb2 also contributes to non-histaminergic itch [53^{••}]. As compared to IgE-FcεRI signaling, Mrgprb2-activated mast cells released more tryptase (but less histamine and serotonin) and excited distinct itch-sensory neuron populations expressing Mrgprd, Mrgpra3, or HTR1F. (b) The secretion of IL-5 in response to the penetration of allergens in the lungs activates IL-5 receptor on nociceptors that in turn release the neuropeptide vasoactive intestinal peptide (VIP) [57]. Allergens also stimulate sensory neurons to release neuromedin U (NMU). Such neuropeptides activate innate lymphoid cell 2 (ILC2) through VIP receptor 2 (VPAC-2) and NMU receptor 1 (NMUR1), and favor the development type 2 lung inflammation [55].

interesting to consider an updated version of the etiology of AD by focusing on neuro-immune crosstalk before the development of pathogenic type 2 immunity.

The communication between sensory neurons and MCs is in fact bidirectional. In a recent article [53^{••}], Meixiong *et al.* used intravital calcium imaging to examine sensory neurons activation in the context of non-histaminergic itch. While canonical IgE/FcεRI-mediated MC activation in the skin mainly triggered the activation of histamine (and capsaicin)-sensitive H₁R⁺ sensory neurons, Mrgprb2-mediated MC activation resulted in the broad excitation of Mrgprd⁺, Mrgpra3⁺, and 5ht1f⁺ sensory neurons, three subpopulations of well-defined NP pruriceptors [15]. Such difference in the activation of neuronal subsets resulted, at least in part, from a differential release of MC granule-associated pruritogens: high proportion of histamine and serotonin via FcεRI, and of tryptase (and maybe other proteases) via Mrgprb2 (Figure 1a). It is generally thought that skin MCs would be primarily involved in histaminergic itch. However, many chronic itch conditions are refractory to histamine antagonists, including AD and allergic contact dermatitis (ACD). Interestingly, the PAMP1-20 neuropeptide is upregulated in skin lesion of patients with ACD and is a well-known agonist of Mrgprb2/X2. In line with these data, using three separate models of allergic skin inflammation, Meixiong *et al.* reported that *Mrgprb2*^{-/-} animals exhibited significantly less itch compared with WT mice [53^{••}]. Consequently, it is very tempting to speculate that PAMP1-20-mediated MRGPRX2 activation is a major mechanism of MC-dependent non-histaminergic itch in patients with ACD.

In addition to differential pathways by which MCs trigger histaminergic and non-histaminergic itch, respectively, Wang *et al.* recently identified that AD-associated inflammation activates basophils in the blood. Upon sensitization to allergen, in this context, basophils are prone to enhance their ability to respond to IgE, resulting in a distinct basophil-sensory neuronal itch axis that is linked by the production of leukotriene C4 from basophils [54^{••}]. Thus, basophils are capable of overriding the histaminergic processes triggered by MCs to elicit other distinct itch pathways.

Emerging role of sensory neurons in allergic lung inflammation

Wallrapp *et al.* reported an interaction between type 2 innate lymphoid cells (ILC2s) and neuromedin U (NMU)⁺ neurons, in models of allergic lungs inflammation [55]. The authors profiled mouse lung-resident ILCs using scRNAseq and found that the neuropeptide receptor Nmur1 was preferentially expressed by ILC2s at steady state and after IL-25 stimulation. NMU, the ligand of NMUR1, activated ILC2s *in vitro*, and *in vivo* co-administration of NMU with IL-25 strongly amplified

allergic inflammation (Figure 1b). Loss of NMU-NMUR1 signaling reduced ILC2 frequency and effector function, and altered transcriptional programs following HDM challenge *in vivo*.

The Vasoactive Intestinal Peptide (VIP) commonly induces smooth muscle cell relaxation, regulates blood flow and can trigger the secretion of water and electrolytes in the gastrointestinal tract [56]. A study by Talbot *et al.* reported that Nav1.8⁺ sensory neurons (part of which are TRPV1⁺ nociceptors) favored the recruitment of ILC2s in models of allergic asthma [57]. They reported that production of IL-5 activated sensory neurons to secrete VIP that further activated ILC2s and effector CD4⁺ T cells via the VIP-VIP receptor 2 (VPAC2) axis to produce inflammatory cytokines, and amplified the pathological features associated with mouse models of type 2 airway inflammation [57] (Figure 1b). Using optogenetics, the same group recently showed that vagal sensory neuron mediated mucus secretion in the mouse trachea during airway inflammation and that this phenomenon was dependent on SP secretion [58[•]]. These findings add more evidence to the pro-inflammatory role played by TRPV1⁺ neurons in enhancing bronchial hyperresponsiveness. Data from patients with asthma also show significant levels of neuropeptides in bronchoalveolar lavage fluids [59] and lungs are densely innervated by sensory neurons [60,61] expressing TRPV1 and TRPA1. Importantly, the fact that pharmacological silencing of pain fibers using treatment either with QX-314 (quaternary derivative of lidocaine [58[•],62]), a cationic derivative of an N-type calcium channel-inhibitor [63] or GDC-0334, a highly potent, selective, and orally bioavailable TRPA1 antagonist [64[•]], could reduce pathological features in a model of lung allergic inflammation might potentially open new perspectives in the treatment and/or prevention of human asthma.

Future perspectives

Various reports have now demonstrated that bidirectional dialogues between sensory neurons and immune cells can impact on the development of frequent allergic skin and lungs disorders. In addition, three studies have suggested that intrinsic primary afferent neurons [65] and neuroimmune interactions [66^{••},67] in the intestine could also contribute to the pathophysiology of food allergy. Production of the neuritin protein, that targets B cells, by follicular regulatory T cells has also recently emerged as a potential mechanism to suppress IgE-mediated allergies by limiting IgE class switch recombination [68^{••}]. Finally, three recent reports also opened new very promising areas of investigation by showing that lymph nodes were innervated by a unique subset of sensory neurons that might regulate local gene expression [69^{••}], that the innate immune regulator STING, a sensor of self-derived and pathogen-derived DNA could control nociception via type I interferon

signaling [70**] and finally that nociceptors could directly influence the mobilization of haematopoietic stem cells in the bone marrow [71**]. While much remain to be done to understand how nociception and sensory neurons regulate human allergic disorders, the development of next-generation therapeutics specifically targeting neuroimmune crosstalk is an exciting area of exploration for the future.

Author contributions

All authors participated in writing and/or editing the paper.

Conflict of interest statement

N.G. is acting as Chief Scientific Officer consultant for Genoskin. He is a member of the scientific advisory board for MaxiVAX. He has served as consultant for Boehringer Ingelheim, GlaxoSmithKline, Escient Pharmaceuticals and Novartis. He has a patent pending for the treatment of type 2 inflammation and mast cell-dependent disorders. B.S.K. has served as a consultant for AbbVie, ABRAX Japan, Almirall, AstraZeneca, Cara Therapeutics, Daewoong Pharmaceutical, Incyte Corporation, LEO Pharma, Lilly, Maruho, Menlo Therapeutics, OM Pharma, Pfizer, and Third Rock Ventures. He has also participated on the advisory board for Almirall, Boehringer Ingelheim, Cara Therapeutics, Kiniksa Pharmaceuticals, Menlo Therapeutics, Regeneron Pharmaceuticals, Sanofi Genzyme, and Trevi Therapeutics. He is stockholder of Locus Biosciences. M.T. has served as consultant or speaker for Sanofi Genzyme and F.W. declare no competing interests.

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