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Neuro-immune interactions in allergic diseases: novel targets for therapeutics

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Abstract

Recent studies have highlighted an emerging role for neuro-immune interactions in mediating allergic diseases. Allergies are caused by an overactive immune response to a foreign antigen. The peripheral sensory and autonomic nervous system densely innervates mucosal barrier tissues including the skin, respiratory tract and gastrointestinal (GI) tract that are exposed to allergens. It is increasingly clear that neurons actively communicate with and regulate the function of mast cells, dendritic cells, eosinophils, T_h2 cells and type 2 innate lymphoid cells in allergic inflammation. Several mechanisms of cross-talk between the two systems have been uncovered, with potential anatomical specificity. Immune cells release inflammatory mediators including histamine, cytokines or neurotrophins that directly activate sensory neurons to mediate itch in the skin, cough/sneezing and bronchoconstriction in the respiratory tract and motility in the GI tract. Upon activation, these peripheral neurons release neurotransmitters and neuropeptides that directly act on immune cells to modulate their function. Somatosensory and visceral afferent neurons release neuropeptides including calcitonin gene-related peptide, substance P and vasoactive intestinal peptide, which can act on type 2 immune cells to drive allergic inflammation. Autonomic neurons release neurotransmitters including acetylcholine and noradrenaline that signal to both innate and adaptive immune cells. Neuro-immune signaling may play a central role in the physiopathology of allergic diseases including atopic dermatitis, asthma and food allergies. Therefore, getting a better understanding of these cellular and molecular neuro-immune interactions could lead to novel therapeutic approaches to treat allergic diseases.

Keywords: allergic inflammation, bronchoconstriction, itch, nervous system, neuro-immunology

Introduction

Allergic diseases are some of the most prevalent disorders of the immune system, with ~50 million people in the USA suffering from nasal allergies (1). There is a rich history of research into the underlying basic and clinical mechanisms of allergies. Recently, studies have uncovered a potentially important role for the nervous system and neuro-immune interactions in the development of the allergic reactions. Although many aspects of neural regulation of allergic inflammation remain unknown, we will highlight recent discoveries and potential future directions in this nascent research area.

Allergies are the consequence of an aberrant response from the immune system to a foreign and relatively innocuous stimulus such as pollen or nut proteins. Allergic responses vary from severe acute physiological reactions such as anaphylaxis to chronic manifestations including asthma or atopic dermatitis (AD) that can manifest through a wide range of symptoms such as sneezing, coughing, itch, edema or vomiting (2). The allergic reaction is dependent on IgE antibodies. Initial exposure to an allergen induces its uptake by professional antigen-presenting cells, which then display complexes of peptide plus MHC class II to antigen-specific T cells, inducing proliferation and expansion into T_h2 cells that secrete cytokines including IL-4, IL-5 and IL-13. IL-4 induces B cells to class-switch to the IgE isotype, whereas IL-5 plays a key role in proliferation of eosinophils. Mast cells and basophils bind allergen-specific IgE via their high-affinity receptor, FcεRI. Upon re-exposure to the allergen and recognition by this bound IgE, sensitized mast cells degranulate, releasing histamine and many other pro-inflammatory mediators including proteases, prostaglandins and leukotrienes, which drive allergic inflammation (2–4). The tissue type and allergen involved dictate distinct cellular and organ-specific physiological responses. Allergic reactions can occur throughout the body. For example, anaphylaxis is characterized by an

acute, systemic and life-threatening state of shock due to a sudden fall in blood pressure caused by mast cell-mediated vasodilation and airway obstruction (5). Allergic rhinitis and asthma are, by contrast, chronic conditions characterized by bronchoconstriction and mucus secretion in the airways (6). AD is characterized by chronic itch, inflammatory skin lesions and increased epidermal thickness (7). In the gastrointestinal (GI) tract, allergic reactions to food are manifested by increased peristalsis, mucus production and diarrhea (8).

The nervous system is involved in regulating all of the major physiological and clinical manifestations listed above. Furthermore, because the nervous system densely innervates all of these tissues, neurons are positioned to directly interact with immune cells to mediate allergic inflammation.

The peripheral nervous system and interactions with allergic tissue

The peripheral nervous system is composed of the somatosensory nervous system (SNS) and the motor system, which densely innervate barrier tissues that are constantly exposed to allergens: the skin, the respiratory tract and the GI tract. The SNS mediates important sensory functions including touch, proprioception, pain and itch. The motor system consists of somatic and autonomic branches: somatic motor neurons mediate the relaxation and contractility of muscles, while the autonomic nervous system is further divided into parasympathetic, sympathetic and enteric arms.

Parasympathetic neurons mediate resting functions such as salivation, lacrimation and digestion. The sympathetic system mediates the 'fight-or-flight response', leading to increased heart rate and decreased digestion, generally functioning in opposition to the parasympathetic system. Finally, the enteric nervous system (ENS), which is contained within the GI tract, mediates gut motility. All these neurons have been found to communicate with the immune system through their release of molecular mediators from their peripheral nerve terminals that act on adaptive or innate immune cells. We describe below the basic anatomy and innervation of different barrier tissues (skin, respiratory tract, GI tract) to facilitate the understanding of neuro-immune interactions in allergic reactions.

Innervation of the skin

The skin is primarily innervated by primary somatosensory afferent neurons (Fig. 1A). These neurons have their cell bodies housed in the dorsal root ganglia (DRG), which innervates the trunk of the body, or in the trigeminal ganglia (TG), which innervates the face and oral cavity. The DRG neurons project to the central nervous system (CNS) in the dorsal horn of the spinal cord, whereas TG neurons project to the trigeminal nuclei of the brainstem. Some somatosensory afferent neurons detect innocuous stimuli (mechanical and thermal), leading to the sensations of touch and temperature, whereas other somatosensory neurons, called nociceptors, detect noxious stimuli (mechanical, thermal or chemical) and induce pain as a protective mechanism.

Somatosensory neurons are very heterogeneous and can be classified by different cellular characteristics (size, conduction velocity, myelination) or by molecular characteristics [expression of transient receptor potential (TRP) channels, growth factor receptors, transcription factors] (9, 10). The expression of neuropeptides by somatosensory neurons is another type of cellular classification related to neuro-immune communication, because vascular and immune cells are able to respond to these neuropeptides. Neuropeptides, including calcitonin gene-related peptide (CGRP) and substance P (SP), are short amphipathic peptides that are stored in dense-core vesicles and released upon calcium influx into peripheral nerve terminals. They have potent vasodilatory and immunomodulatory actions. Peptidergic nociceptors express neuropeptides including CGRP, SP and vasoactive intestinal peptide (VIP). The development of peptidergic nociceptors is mediated by the tyrosine kinase receptor A (TrkA), the receptor for nerve growth factor (NGF), and they innervate the dermis/epidermis border (11). Non-peptidergic nociceptors, by contrast, do not express neuropeptides and innervate more superficial layers of the epidermis (12).

Innervation of the respiratory tract

The respiratory tract receives somatosensory afferent innervation from neurons that reside within the DRG, as well as vagal sensory innervation from neurons of the nodose ganglia/jugular ganglia (NG/JG) (Fig. 1B). While DRG neurons mediate pain and somatosensation, NG/JG neurons mediate cough, bronchoconstriction, nausea, vomiting and other visceral sensations. Pulmonary mechanoreceptors from the NG are myelinated non-peptidergic neurons that are sensitive to the stretch of the lungs (inflation and deflation) [for an extensive review on this topic, see ref. (13)]. Pulmonary chemosensors are unmyelinated NG or JG neurons that detect different chemical agents including noxious stimuli and a subset of these chemosensory neurons express neuropeptides including CGRP and SP (14).

The lung also receives efferent innervation by postganglionic cholinergic neurons from the parasympathetic nervous system. These cholinergic neurons mediate bronchoconstriction. By contrast, efferent innervation by postganglionic noradrenergic neurons from the sympathetic system mediates bronchodilation. Much of the function of lung-innervating neural circuits remains to be fully defined, but it is clear that sensory afferent neurons of the vagus nerve transduces signals to the brainstem that could set off motor reflexes back to the lung through the parasympathetic or sympathetic branches, leading to bronchial, inflammatory or vascular regulation.

Innervation of the GI tract

Finally, the GI tract is the only organ in the body that possesses its own self-contained nervous system, called the ENS (Fig. 1C). The GI tract is also densely innervated by extrinsic neurons that are outside of the GI tract. The intrinsic neurons of the ENS consist of both sensory and motor arms. The cell bodies of intrinsic enteric neurons are situated in two plexi along the digestive tract: the myenteric plexus and the submucosal plexus. The sensory neurons of the ENS are the intrinsic primary afferent neurons (IPANs), which respond to nutrient changes in the gut lumen, gut microbes and mechanical distortion. They then send reflex signals through enteric interneurons and motor neurons to coordinate gastric secretion and gut motility (15, 16).

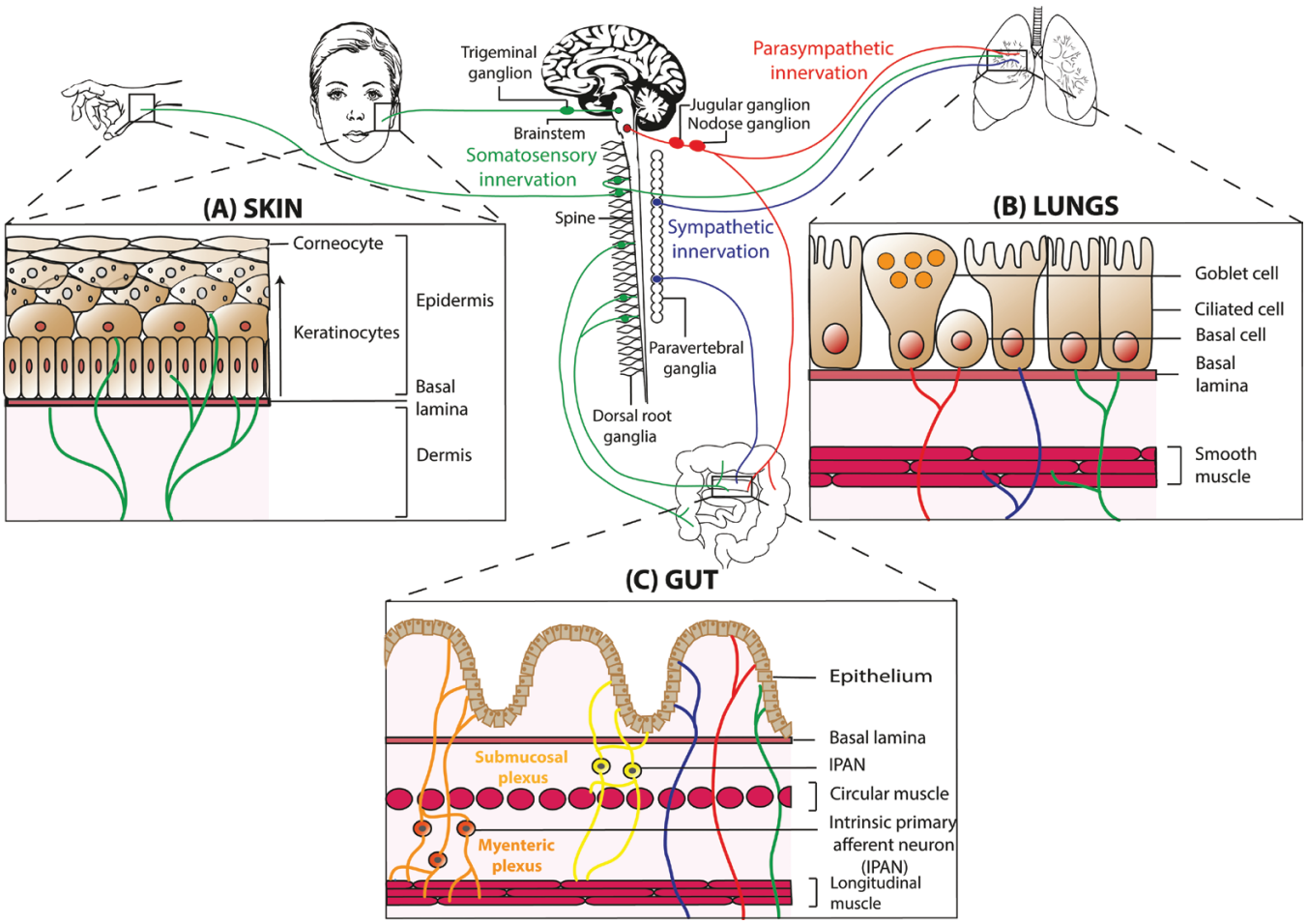

Fig. 1. Neuroanatomy and innervation of the skin, the lungs and the GI tract. (A) The SNS densely innervates the skin (dermis and epidermis) and these sensory neurons mediate itch, pain and mechanosensation. Somatosensory neurons innervating the body have their cell bodies in the DRG, with central projections to the spinal cord. Somatosensory neurons innervating the face have their cell bodies in the TG, with central projections to the brainstem. (B) The lungs are densely innervated by both the SNS and the autonomic nervous system (ANS), which mediate irritant detection, cough, bronchoconstriction and breathing. Sensory neurons that innervate the lung have their cell bodies in the thoracic DRG or the NG/JG. The ANS that innervates the lung is composed of parasympathetic neurons, whose cell bodies reside in the brainstem and innervate the lung via the vagus nerve, and of sympathetic neurons, whose cell bodies reside in the paravertebral ganglia. (C) The GI tract has a self-contained nervous system called the ENS, which is formed by IPANs, interneurons and motor neurons grouped in the myenteric and the submucosal plexuses. The GI tract is also innervated by extrinsic sensory nerve fibers originating in the DRG and vagus nerve that send the afferent information to the CNS. Parasympathetic and sympathetic nerves also send efferent information from the CNS to the gut by signaling to the ENS to mediate nutrient sensation, mucus production and gut motility.

The extrinsic sensory neurons that innervate the GI tract come from two external sources: the spinal neurons with their cell bodies in the DRG and the vagal neurons with their cell bodies in the NG/JG. Spinal somatosensory neurons that mainly innervate the colon transmit visceral sensations to the dorsal horn of the spinal cord including thermal sensation, mechanical sensation and pain. Vagal neurons that mainly innervate the small intestine transmit non-painful visceral sensations including nutrient detection, satiety and nausea to the nucleus of the solitary tract in the brain stem. The GI tract is also innervated by autonomic neurons, including parasympathetic efferent neurons through the vagus nerve and sympathetic efferent neurons through the superior mesenteric and celiac ganglia. The extrinsic and intrinsic neurons that innervate the gut communicate with each other via neurotransmitters and neuropeptides, thus coordinating key functions such as nutrient sensation, digestion and GI motility.

Neurogenic inflammation and neuro-immune cross-talk in allergic reactions

One of the first indications that the nervous system played an active role in regulating inflammation was observations by Bayliss in 1901, who found that stimulation of the root of DRG neurons induced vasodilatation in the limb (17). This function he referred to as antidromic conduction, where afferent nerves gain efferent function, is mediated by the back-propagation of action potentials and axonal reflexes that results in CGRP and SP release at peripheral nerve terminals. These neuropeptides then act on the vasculature and immune system to produce vasodilatation, plasma extravasation, edema

and immune cell recruitment and activation (18, 19). This led to the concept that neuronal signaling can produce a 'neurogenic inflammation' [for review, see ref. (20)]. It is increasingly clear that neuronal regulation of immunity plays an important role in the context of allergic inflammation.

Recently, a multitude of two-way interactions between neurons and immune cells have been discovered, due in part to the proximity between nerve fibers and immune cells in mucosal and barrier tissues. Mast cells, which are essential for allergic responses, are in close contact with nerves in the skin (21), in the GI tract (22, 23) and in the airways (24). Some mast cells are able to form direct contacts and attachments with nerves through the cell adhesion molecule 1 (CADM1) (25, 26). In certain allergic pathologies such as allergic rhinitis or AD, the number of associations between mast cells and neurons increases during inflammation (24, 27). Dendritic cells (DCs) are also found closely apposed to the peripheral nerve terminals of vagal sensory neurons in the airways (28, 29) and these interactions are increased in allergic airway inflammation (29). Eosinophils, a key innate effector cell type in allergic reactions, have also been found to localize close to cholinergic nerves in antigen-challenged animals in allergic airway inflammation (30, 31).

Immune cells act on sensory neurons to mediate allergic processes driven by the nervous system including itch and bronchoconstriction. Sensory neurons possess receptors for cytokines, growth factors and other inflammatory mediators secreted by allergic-type immune cells. Neurons secrete mediators including neuropeptides and neurotransmitters, which act on their cognate receptors on allergic-type immune cells to drive or regulate immunity. These bidirectional neuro-immune interactions occur early and could have a huge impact on the development of the allergic inflammation. Thus, understanding and targeting these neuro-immune interactions could lead to novel approaches to treat allergic disease conditions.

Neuro-immune communication in itch and skin allergies

Skin allergic reactions usually involve rashes, redness and itching and can be caused by immune reactions to chemicals (e.g. urushiol in poison ivy), food, medications or environmental allergens such as house dust mites. AD (also known as eczema) is a chronic skin condition caused by aberrant skin allergic responses. The cross-talk between the immune system and the nervous system is extensive in AD and other skin allergic conditions and it is increasingly clear that these interactions drive itch and inflammation. Below, we highlight some of the key molecular mechanisms discovered to be involved in these neuro-immune interactions and how they are being targeted to treat allergic skin diseases.

Immune-mediated neuronal activation and itch

Itch is a sensation that is closely associated with skin allergies. It is a neuron-driven reflex with the purpose of scratch-mediated removal of threats from the skin such as a parasite or an insect. The mechanisms of itch and pruritus (inflammatory itch) are complex; for a more extensive review of its molecular and cellular mechanisms, please see ref. (32).

Pruriceptor neurons are the subtype of somatosensory neurons that mediate itch and, like nociceptors, their cell bodies reside in the DRG and their nerve terminals innervate the skin. Many of the inflammatory mediators released by allergic-type immune cells (mast cells, eosinophils, T_h2 cells) can act on pruriceptor neurons to sensitize itch. For example, pruriceptor neurons possess receptors for, and respond to, histamine, serotonin (5-HT), lipids, cytokines and growth factors (Fig. 2A). The itch–scratch cycle could lead to skin damage, increased allergen exposure and exacerbation of inflammation. Therefore, a better understanding of the neuro-immune mechanisms of allergic itch could result in better treatments for AD or other skin conditions.

Histamine and itch

Histamine, released by mast cells, was one of the first molecular pruritogens to be identified. Histamine-induced itch is mediated by the histamine receptor 1 (H1R) on pruriceptor neurons and its activation leads to Gq-coupled downstream signaling through the transient receptor potential V1 (TRPV1) cation channel (33) (Fig. 2A). However, antihistamines targeting H1R often do not relieve itch, in particular in chronic itch conditions such as AD (34). More recently, studies showed that targeting the histamine receptor H4R was more efficient to alleviate histamine-induced itch (35) and the combined treatment with H1R and H4R antagonists ameliorated the pruritus and the dermatitis in a mouse model of chronic allergic dermatitis (36).

One clinical trial showed that JNJ-39758979, a potent selective H4R antagonist, was able to inhibit histamine-induced itch in healthy human subjects (37). In a second clinical trial, which was terminated early because of off-target adverse effects, JNJ-39758979 showed promising though not conclusive results in alleviating pruritus in AD patients (38). A combination of H1R and H4R antagonism might be a good strategy to treat AD patients in the future. However, it is also likely that many itch mechanisms in skin allergies are non-histaminergic in nature, necessitating further research.

Thymic stromal lymphopoietin and itch

Thymic stromal lymphopoietin (TSLP) is a cytokine produced by epithelial cells (e.g. keratinocytes) during allergic diseases and is a key driver of skin allergic inflammation. TSLP levels are elevated in the skin of AD patients (39). TSLP activates DCs to induce production of the chemokines CCL17 and CCL22, which attracts T_h2 cells to the skin (40) (Fig. 2A). Transgenic over-expression of TSLP in keratinocytes triggers skin and systemic AD-like pathologies (41, 42).

Recently, Wilson *et al.* showed that TSLP can directly activate a subset of DRG sensory neurons by calcium influx. They found that TSLP injection into mice induced scratching behavior, which was dependent on its receptor, composed of TSLPR and IL-7Rα, expressed in neurons (43). This pruriceptor activation was dependent on coupling of the TSLP receptor to the TRPA1 cation channel. They further showed that TSLP release from keratinocytes was stimulated by the activation of protease-activated receptor 2 (PAR-2) by its agonists SLIGRL (a peptide) and tryptase (43). Thus, keratinocytes release TSLP during atopic diseases such as AD and this can act directly on pruriceptor neurons to induce itch signaling.

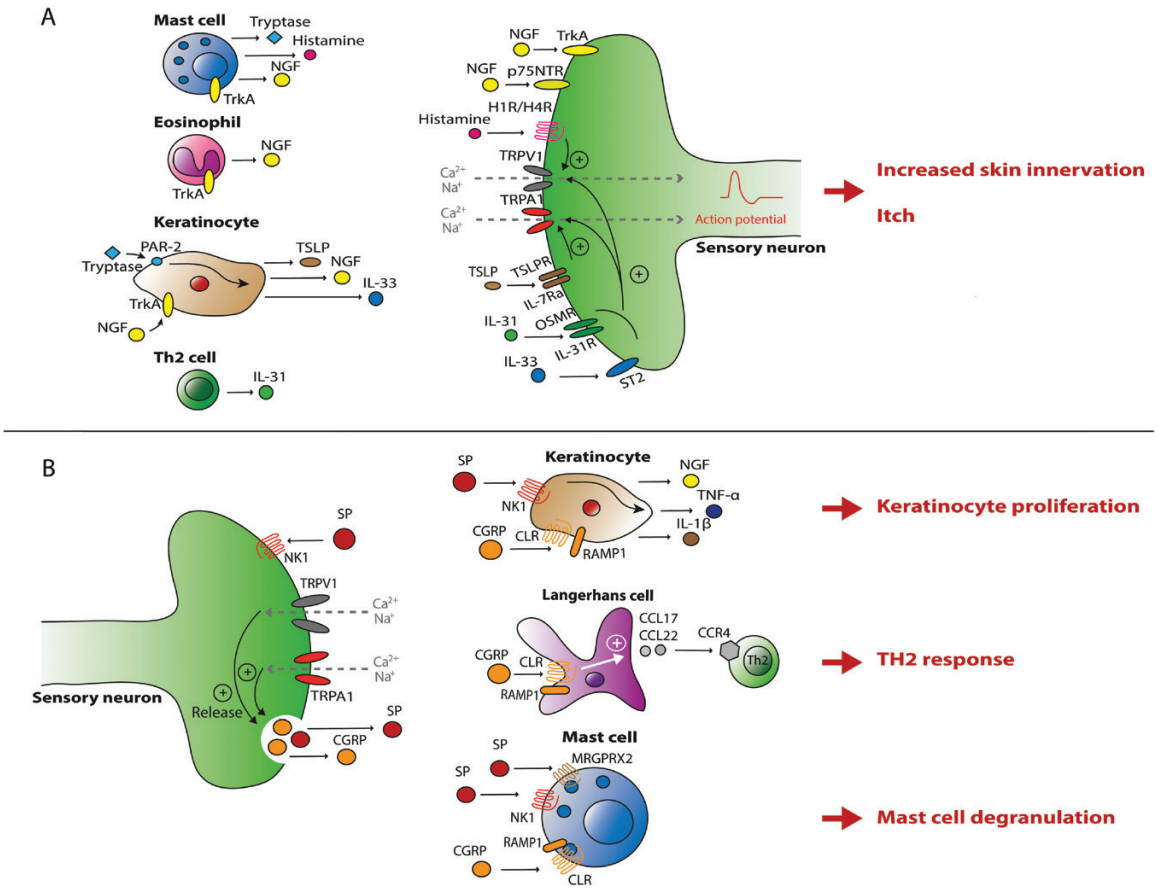

Fig. 2. Cross-talk between neurons and immune cells in allergic skin inflammation. (A) Immune-mediated activation of neurons in the skin: here, we illustrate how allergic-type immune cells release molecular mediators and cytokines that act directly on sensory neurons in skin inflammatory conditions such as AD. The functional result of this immune to neuron signaling is increased innervation and itch. Mast cells, eosinophils and keratinocytes release the neurotrophin NGF, which binds to the high-affinity receptor TrkA and the low-affinity receptor p75NTR on neurons, which can induce increased skin innervation. Mast cells release histamine, which binds to neuronal GPCRs H1R and H4R, which in turn amplifies its downstream signaling through the TRPV1 ion channel to induce neuronal activation and itch. Keratinocytes release the cytokine TSLP in response to cleavage of PAR-2 by tryptases released in allergic skin diseases. TSLP then binds to neuronal TSLPR–IL-7Ra, which in turn is coupled to TRPA1 ion channel signaling to produce itch. Finally, T_h2 cells produce the cytokine IL-31 in AD lesions, which mediates itch by binding to its receptor composed of IL-31R and OSMR on neurons. IL-31-mediated neuronal activation is also coupled to both the TRPV1 and TRPA1 ion channels. (B) Neuron-mediated activation of immune cells in the skin: neurons release mediators that act directly on immune cells to modulate inflammation during skin allergies. Sensory neurons that innervate the skin release the neuropeptides SP and CGRP from their nerve terminals. NK1, the receptor for SP, is expressed on keratinocytes, where its activation triggers the release of NGF, TNF-α and IL-1β. Mast cells express both NK1 and MRGPRX2, an Mrgpr receptor that responds to SP, where their activation by SP induces mast cell degranulation. The receptor for CGRP, which is composed of a complex of CLR and RAMP1, is also present on mast cells and its activation triggers degranulation. CGRP induces Langerhans cell cytokine polarization, where it increases the release of CCL17 and CCL22 and decreases the release of CXCL9 and CXCL10, thus favoring T_h2 cell recruitment and responses. Therefore, neurons can mediate immune cell responses through neuropeptides.

Interleukins and itch

IL-31 is a specific cytokine highly expressed by T_h2 cells in AD (44). The cognate receptor for IL-31 is composed of IL-31RA and the oncostatin M receptor (OSMR), which are both expressed by pruriceptor sensory neurons that mediate itch and by skin keratinocytes (9, 10) (Fig. 2A). In mice, intradermal injections of IL-31 induce itch-associated behaviors (45). Moreover, IL-31 mRNA is increased in the lesional skin of AD patients (45, 46), and serum levels of IL-31 were shown to correlate with the disease activity in AD (47). Therefore, T_h2 cells likely release IL-31 during allergic skin inflammation, which acts to sensitize pruriceptor neurons to produce itch. IL-31 may thus be an interesting target for the treatment of itch in AD. Indeed, in a recent clinical trial, Ruzicka *et al.* showed that nemolizumab, a humanized antibody against IL-31RA, improved pruritus in patients with AD, supporting future studies of IL-31 as a potential therapeutic target in chronic inflammatory itch (48).

IL-33 is another key driver of allergic inflammation that is released by keratinocytes and acts to drive type 2 immunity. Interestingly, in a urishiol-induced model of allergic contact dermatitis (ACD), Liu *et al.* showed that IL-33, acting on its receptor ST2 expressed on DRG neurons, induces itch in sensitized mice (49). The activation of neurons by IL-33 is mediated by both TRPV1 and TRPA1 ion channels. They further showed that treatment with IL-33- or ST2-neutralizing antibodies reduced the dermatitis phenotype induced by urushiol. Therefore, both IL-31 and IL-33 are able to directly sensitize sensory neurons.

Mrgpr members and itch

Several members of the family of the Mas1-related G protein-coupled receptors (MRGPRs) have been identified on sensory neurons as responding to different types of pruritogens [for review, see ref. (50)]. This family has >50 members in mice, subdivided in MrgprAs, MrgprBs, MrgprCs and MrgprD-H. In humans, this family only has 10 members and is called MRGPRX. So far, three members have been identified as pruriceptive receptors. MrgprA3, and its human homolog MRGPRX1, is responsible for neuronal activation and scratching behavior induced by chloroquine, an antimalarial drug that undesirably triggers itch (51); MrgprC11 mediates itch induced by BAM8-22, a bovine adrenal medulla peptide, and by SLIGRL, a synthetic peptide (52, 53); and β-alanine induces itch through MrgprD (54). Both MrgprA3- and Mrgprc11-mediated itch are dependent on the TRP channel TRPA1 (53). The endogenous agonists are yet unknown for most of these receptors and their role in pathologies involving chronic itch such as AD is the subject of current research.

Sensory neuron TRP channels in itch

As we have discussed previously, members of the TRP cation channels family, particularly TRPV1 and TRPA1, are involved in the amplification and gating of pruriceptive signals in sensory neurons. TRPV1 is a prototypic large-pore cation channel that is activated by noxious heat, low pH, and it is sensitized through G protein-coupled receptors (GPCRs) that are linked to inflammatory mediators, including the histamine receptors. TRPA1 is another large-pore cation channel in nociceptor neurons that detects noxious chemicals and electrophiles (55).

As we saw before, TRPV1 mediates histamine-dependent itch while TRPA1 mediates histamine-independent itch including TSLP-induced itch (33, 43). It was further shown that TRPA1 is necessary for the development of chronic itch in certain models. In a dry skin model of itch, $TRPA1^{-/-}$ mice developed a weak itch and inflammatory phenotype (scratching, skin thickness) compared to wild-type mice (56). In the same study, gene expression was measured in skin biopsies after dry skin induction. The up-regulation of genes coding for inflammatory mediators including IL-31Ra and IL-33 was dependent on TRPA1. In a model of ACD induced by oxazolone, $TRPA1^{-/-}$ mice displayed strongly diminished dermatitis pathology: diminished skin thickness, protein levels of inflammatory cytokines (CXCL2, IL-4 and IL-6) and scratching behavior (57). Thus, TRPA1 seems to have a major role in the neuro-immune cross-talk in pathologic skin allergies and could be a potential target for new therapies in allergic dermatitis.

NGF in driving skin inflammation and itch

NGF is a neurotrophin that has been linked to both itch and skin allergies. Neurotrophins are growth factors [NGF, brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3) and neurotrophin 4 (NT-4)] involved in the differentiation, innervation and survival of neurons (58). Keratinocytes are the main source of NGF in the skin (59). NGF is also expressed and secreted by immune cells including eosinophils and monocytes during inflammation (60–62) (Fig. 2A). NGF binds to its receptor TrkA and to the low-affinity neurotrophin receptor p75NTR, which are expressed on pruriceptor neurons, nociceptor neurons, as well as on eosinophils and mast cells (63, 64).

While TrkA is not detected in keratinocytes from healthy subjects (59, 65), in AD patients, TrkA is expressed in keratinocytes and this expression is increased during inflammation, where it is thought that NGF promotes keratinocyte proliferation (66). Importantly, NGF is known to increase cutaneous innervation in a mouse model of AD and could thus mediate the development of chronic itch (67). Treatment with a neutralizing antibody against NGF inhibited the development of skin lesions, epidermal innervation and scratching behavior in AD mice (67). In AD patients, serums levels of NGF, as well as the neurotrophin BDNF and the neuropeptides SP, CGRP, VIP and neuropeptide Y (NPY), have been found to be elevated (68–70). Thus, NGF could be a target for future treatment of itch and allergic inflammation in AD.

Neuronal mediation of skin inflammation through SP and CGRP

Neuro-immune communication in the skin is mediated by the neuropeptides SP and CGRP. Upon activation, peptidergic sensory neurons release SP and CGRP from their nerve terminals, which can then act on immune cells (Fig. 2B). The number of SP/CGRP fibers in the skin of AD patients increases during allergic inflammation, suggesting a role for these neuropeptides in the pathophysiology of skin allergies (71).

SP induces the degranulation of mast cells and the release of inflammatory mediators such as prostaglandin D2 (PGD2), histamine, leukotrienes, serotonin (5-HT) and tryptases (72). Intra-dermal injections of SP in humans results in a wheal and flare reaction, which is mediated by mast cells (20, 72). SP also induces keratinocytes to release pro-inflammatory mediators including TNF-α, IL-1β and NGF (73). SP acts on the vasculature to cause plasma extravasation and edema. Finally, SP injections can induce a scratching behavior in mice that is dependent on TRPA1 channels (57).

The receptors responsible for the actions of SP are a subject of discussion in the literature. SP binds to the neurokinin-1 receptor (NK1) expressed on keratinocytes and vascular smooth muscle cells (74, 75). The expression of NK1 on mast cells is still controversial and whether the SP-induced degranulation is dependent on NK1 has been debated (76). A study reported that NK1 is expressed only in certain rat strains (77) and NK1 mRNA was also detected in cultured RBL-2H3 cells, a rat mast cell line (78). Interestingly, another study showed that NK1 expression in bone marrow-derived mast cells was low but that its expression increased when the cells were stimulated by factors present during allergic inflammation including IL-4 and stem cell factor (79). Treatment with NK1 antagonists has given contrasting results depending on the studies. NK1 antagonists either have no effects or block only partially SP-activation of human mast cells (80–82). They showed disparate results in treating pruritus in patients with atopic conditions: beneficial in some cases (83, 84) or without effects in others (85, 86). It was then proposed that SP could induce its effect through a different pathway. Recent studies have shown that SP can also act on mast cells through MRGPRX2, another type of receptor

belonging to the Mas-related family of GPCRs, to induce mast cell degranulation (87–91). McNeil *et al.* found that human MRGPRX2, or its mouse ortholog MrgprB2, is present in mast cells and responds to a variety of basic secretagogues including SP, VIP, the antimicrobial peptide LL-37 and the canonical mast cell activator 48/80 to induce degranulation [for review, see refs (89) and (90)]. Knockdown of MRGPRX2 in human mast cells or mutation of MrgprB2 in murine mast cells inhibited SP-induced mast cell degranulation (82, 90). Gaudenzio *et al.* found that MrgprB2^{MUT} mice showed a 50% reduction in vascular leakage induced by SP intra-dermal injection; however, total mast cell-deficient mice showed a complete abrogation of SP-induced responses, indicating potential involvement of another mast cell SP receptor, potentially NK1 (91). In the skin of patients with severe chronic urticaria, expression of MRGPRX2 on mast cells is up-regulated (82). Taken together, these findings suggest that SP-induced effects on mast cells could be mediated by two pathways, and that MRGPRX2 or NK1 may prove to be therapeutic targets in skin allergic conditions.

CGRP acts by binding to a receptor composed of the GPCR CLR (calcitonin receptor-like receptor, also known as CALCRL) and receptor activity-modifying protein 1 (RAMP1). These receptors are expressed on keratinocytes, mast cells, Langerhans cells and vascular endothelial cells (92). CGRP is well known to act on the vasculature to induce vasodilation. Langerhans cells are DCs that reside in the epidermis that drive skin antigen presentation. Ding *et al.* showed that CGRP stimulation causes Langerhans cells to bias their antigen presentation toward a T_h2 response by inducing up-regulation of IL-4 and down-regulation of IFN-γ (93). CGRP also induces mast cell degranulation and keratinocyte proliferation (94, 95).

Neuro-immune communication in asthma and allergic airway inflammation

Allergic airway inflammation is driven by immune responses in the respiratory tract to allergens in the air, such as pollen, house dust mites or molds. The most common types of airway allergic conditions include allergic rhinitis and asthma. These atopic conditions frequently occur together. Symptoms include a runny or congested nose, sneezing, irritable airways, bronchoconstriction, cough, wheezing and shortness of breath. Cough and bronchoconstriction, as well as many of these other symptoms, are direct consequences of neural activation within the airways (96). Recent work has drawn attention to the nervous system and neuro-immune interactions as playing an important role driving or modulating the physiopathology of asthma and allergic rhinitis.

Neurotrophins in allergic airway inflammation

The neurotrophins, NGF and BDNF, are mediators of neuro-immune interactions in the airways. NGF and BDNF levels are increased in animal models of allergic airway inflammation (97) and in the airways of asthma patients (98–100). During inflammation, NGF and BDNF are produced by structural cells of the lungs including epithelial cells and airway smooth muscle cells (ASMCs) and by neurons; NGF is also highly expressed by activated mast cells and eosinophils (Fig. 3A) (58, 101, 102). NGF and BDNF bind to specific receptors, TrkA and TrkB, respectively, as well as the low-affinity neurotrophin receptor p75NTR. These receptors are expressed across the lung epithelium, airway smooth muscles and immune cells, mediating a wide numbers of responses in these cell types [for review, see refs (58,102,103)]. Their receptors are also expressed by sensory neurons, playing a key role in neural growth, survival and sensitization during airway inflammation. Of note, these neurotrophins induced hyperinnervation of the lungs by DRG neurons, and increased their expression of the neuropeptides CGRP and SP (104–106).

In immune cells, neurotrophins participate in the activation of eosinophils and their survival (63, 97); they promote the maturation and polarization of lung DCs toward a T_h2 phenotype (107). Neurotrophins enhance the contractibility of ASMCs (108, 109) and promote their proliferation (110).

NGF infusion also induces airway hyperresponsiveness (AHR) in different animal models of allergic airway inflammation (103). Several studies investigated the therapeutic potential of inhibiting NGF in mouse models of asthma. Anti-NGF neutralizing antibody was found to significantly reduce AHR and inflammation in the mouse model of asthma in which chicken ovalbumin (OVA) induces sensitization (107). Anti-NGF and anti-TrkA neutralizing antibodies were able to reduce collagen deposition in the airways in a model of chronic allergic airway inflammation (111). Administration of a small interfering RNA (siRNA) targeting NGF significantly inhibited AHR, decreased pro-inflammatory cytokines, decreased eosinophilic recruitment and inhibited production of the neuropeptide SP in the lungs in a murine model of allergic asthma (112). Therefore, targeting neurotrophins may be a novel approach to treat allergic airway inflammation.

Interactions between mast cells and neurons in allergic airway inflammation

It is well characterized that histamine, released by mast cells, is a key mediator in allergic inflammatory conditions. Histamine is present in high concentrations in bronchoalveolar lavage fluid (BALF) of patients with allergic asthma and it is known to promote characteristic symptoms of allergic inflammation through both H1R and H4R (113–115). Histamine receptors are expressed in vagal sensory afferent neurons (116), which innervate the lungs. However, the contribution of sensory neurons to histaminergic effects in asthma remains to be elucidated.

Sphingosine-1-phosphate (S1P) is a known mediator of allergies that is released by stimulated mast cells. In the lungs, S1P administration triggers AHR and airway inflammation in mice (117). S1P has autocrine and paracrine effects on immune cells, inducing degranulation, cytokine and lipid production, and migration of mast cells (118). A recent study showed that sensory neurons that innervate the lungs express S1PR3, one of the receptors for S1P (119) (Fig. 3A). They further showed that the AHR induced by an S1PR3 agonist was absent in mice lacking sensory neurons, suggesting that neurons might partially mediate S1P effects in allergic airway inflammation (119).

CGRP in allergic airway inflammation

The neuropeptide CGRP is increased in airways of patients with asthma or allergic rhinitis (120, 121). In the airways, CGRP is released by nodose sensory neurons during inflammation

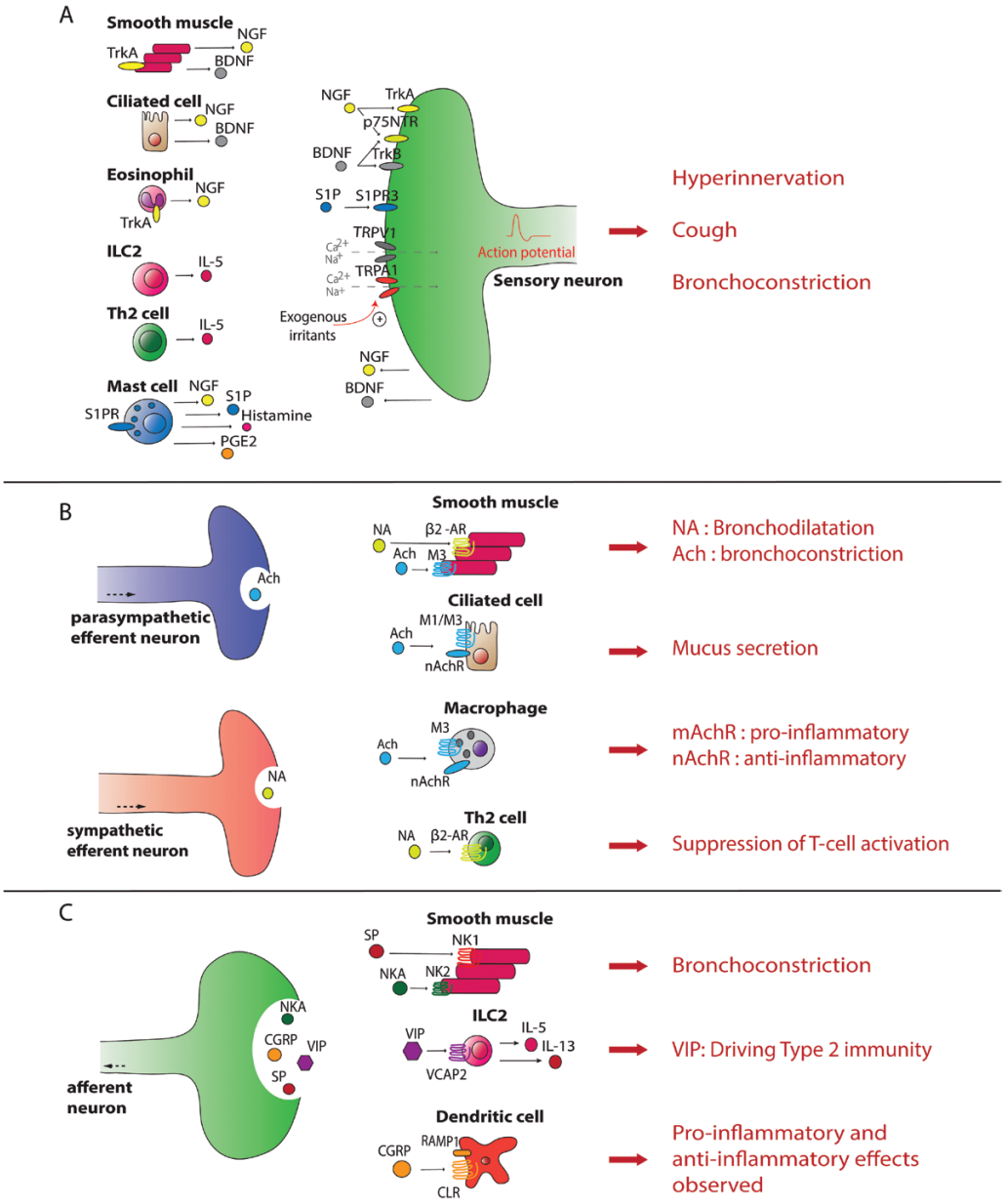

Fig. 3. Cross-talk between neurons and immune cells in allergic airway inflammation. (A) Immune-mediated activation of neurons in the respiratory tract: immune cells release molecular mediators and cytokines that act directly on sensory neurons innervating the lungs in allergic diseases such as asthma or allergic rhinitis. The functional result is hyperinnervation, cough and bronchoconstriction. Mast cells, ciliated cells, eosinophils and smooth muscle cells produce the neurotrophin NGF, which binds to the receptors TrkA and P75NTR expressed by sensory neurons. Ciliated cells, smooth muscle and sensory neurons also secrete the neurotrophin BDNF, binding receptors TrkB and P75NTR expressed by sensory neurons. Mast cells release S1P that binds the receptor S1PR3 on sensory neurons, inducing a hyperinnervation of the lungs, cough and bronchoconstriction. Exogenous irritants, such as tear gases, air pollution or cigarette smoke also act directly on the TRPA1 cation channels expressed by neurons to activate cough and bronchoconstriction. (B) The autonomic nervous system, including parasympathetic and sympathetic branches, releases neurotransmitters to signal to structural cells and immune cells of the lungs. The parasympathetic neurons release Ach that binds the muscarinic receptor M3 on the smooth muscle leading to bronchoconstriction. It can also bind M1, M3 and the nicotinic receptor (nAchR) on ciliated cells, resulting in mucus secretion. Ach has a dual effect on macrophages: binding to its M3 receptor produces pro-inflammatory effects; whereas binding to nAchR produces anti-inflammatory effects. The sympathetic nervous system releases NA that activates the β2-AR expressed by smooth muscles, resulting in bronchodilation. It also binds to β2-AR on T_h2 cells to suppress T-cell activation. (C) The sensory nervous system, including DRG and vagal afferent neurons, releases neuropeptides including SP, NKA, VIP and CGRP that can directly act on the immune system. SP and NKA bind NK1 or NK2, respectively, on smooth muscle cells, leading to bronchoconstriction. VIP binds its receptor VCAP2 on ILC2, inducing the release of IL-5 and IL-13 to drive the type 2 immunity. CGRP binds to its receptor complex CLR–RAMP1 on DCs, which has been found to induce both pro-inflammatory and anti-inflammatory effects depending on the context of lung inflammation.

from their nerve terminals (122) and the CGRP receptor complex CLR–RAMP1 is expressed by lung DCs (123) (Fig. 3C). However, other cell types secrete CGRP in the lungs, such as T cells, macrophages and human airway epithelial cells following the activation of CCR4 by CCL17 (120, 124).

Recent studies have shown contradictory effects of CGRP in driving or modulating airway allergies. On the anti-inflammatory side, administration of CGRP resulted in the normalization of airway responsiveness to inhaled methacholine (125). CGRP inhibited DC maturation and reduced eosinophilic airway inflammation (123). On the pro-inflammatory side, CGRP was shown to alter DC motility (126) and knockout mice for CGRP ($Calca^{-/-}$) or components of its major receptor ($RAMP1^{-/-}$ and $Calcrl^{+/-}$) showed attenuated hyperresponsiveness in OVA antigen-induced models of allergic airway inflammation (127, 128). Therefore, it remains to be determined whether CGRP is pro- or anti-inflammatory in the context of asthma or other airway diseases.

Tachykinins in allergic airway inflammation

Tachykinins are a family of neuropeptides expressed by sensory neurons, including SP as well as neurokinin A (NKA) and neurokinin B (NKB) (Fig. 3C). These neuropeptides are processed proteolytically from common precursors called Tac1 and Tac2 (also known as preprotachykinins). SP, NKA and NKB bind to GPCRs named NK1, NK2 and NK3, respectively. Both tachykinin levels and receptor expression are increased the airways of allergic patients following stimulation with allergen (121, 129–131). Several studies have tested pharmacological antagonists against the tachykinin receptors in the treatment of asthma, either selective (anti-NK1), dual (anti-NK1/NK2) or triple (anti-NK1/NK2/NK3) [for review, see refs (132,133)]. Although a number of these studies showed positive results in attenuating one or several asthma outcomes such as airway responsiveness (AHR, bronchoconstriction) and airway inflammation (eosinophilic influx), more investigations are necessary to understand the mechanisms of action and the specific contributions of the three receptors in the physiopathology of asthma. As we have discussed previously, SP can also act through the receptor MRGPRX2 on mast cells. While lung mast cells express low levels MRGPRX2 (82, 134), the subtype of mast cells that express the receptor is increased in asthma which suggests MRGPRX2 could play a role in the pathogenesis of asthma (135).

VIP in allergic airway inflammation

The neuropeptide VIP is also a key mediator of neuro-immune communication and is classically considered to have anti-inflammatory effects (136). In a recent study, Talbot *et al.* uncovered a role for communication in the respiratory tract between sensory neurons and immune cells through VIP in an OVA-dependent mouse model of asthma (137). They showed that nodose afferent neurons released VIP, which acts on innate lymphoid type 2 (ILC2) cells, which express the VIP receptor VPAC2 (Fig. 3C). In response, ILC2 up-regulate IL-5 production, which in turn drives eosinophil recruitment. Interestingly, they also found that targeting VPAC2 with a specific antagonist also decreased ILC2 activation *in vivo* (137). Therefore, VIP signaling and VPAC2 could be an interesting target for allergic airway inflammation.

Sensory neuron TRP channels in airway inflammation

Neurogenic inflammation, and thus neuropeptides release, can be due in part to the activation of members of TRP channels expressed in airway-innervating sensory neurons, especially TRPA1 and TRPV1 (13). As we previously discussed, TRPA1 detects noxious chemicals and electrophiles, in particular a large number of airborne irritants including tear gases, air pollution or cigarette smoke (138). It is also activated by mediators of inflammation such as bradykinin and prostaglandin E2 (PGE2).

In the OVA-induced mouse model of allergic airway inflammation, either genetic ablation or pharmacological inhibition of TRPA1 greatly reduced AHR, mucus and cytokine production as well as leucocyte infiltration (139). By contrast, a recent study found that TRPV1, but not TRPA1, was involved in a house dust mite-driven mouse model of allergic airway inflammation and an OVA-driven rat model of asthma (140). While the particular contribution of TRP channels remains to be determined in asthma, these studies highlight the potential roles of TRP channels and the neurons that express them in animal models of asthma, especially in the context of neurogenic inflammation.

Silencing sensory neurons to treat airway inflammation

Targeting sensory neurons may be a novel approach to treat AHR and lung inflammation in the pathology of asthma. Tränkner *et al.* recently showed that targeted ablation of a subset of NG/JG sensory afferent neurons expressing TRPV1 prevents the development of AHR in an OVA-induced mouse model of asthma (119). Though AHR was greatly reduced, they did not find major differences in immune cell recruitment in the airways following sensory neuron ablation (119).

By contrast, Talbot *et al.* showed that ablation of sensory neurons expressing the sodium channel Nav1.8 decreased immune cell recruitment in the OVA-induced asthma model (137). They also acutely silenced the sensory neuron activity through administration of QX-314, a charged, membrane-impermeant sodium channel blocker that is a derivative of lidocaine. QX-314 is thought to specifically enter activated sensory neurons through the pores formed by activated TRPV1 and TRPA1 ion channels (141). Talbot *et al.* found that QX-314 treatment after OVA-mediated allergic airway sensitization reduced AHR, T_h2, and ILC2 responses (137). Therefore, silencing lung-innervating sensory neurons is a potential therapeutic target for asthma.

Parasympathetic and sympathetic regulation of allergic airway inflammation

Acetylcholine (Ach) is the main neurotransmitter released by parasympathetic postganglionic neurons in the respiratory tract inducing bronchoconstriction. Two types of acetylcholine receptors (AchRs) bind to Ach: muscarinic receptors mAChR (GPCRs) and nicotinic receptors nAchR (channel receptors). In the airways, AchRs are expressed by structural cells such as ASMCs and epithelial cells, and also by immune

cells such as macrophages and T cells (Fig. 3B) (142, 143). In the physiopathology of asthma, Ach is involved in the airway remodeling by inducing thickening of airway smooth muscle tissue through growth factor-induced proliferation, contractile protein expression and extracellular matrix deposition (144).

A recent paper showed that these effects of Ach were greatly reduced in mice lacking the M3 muscarinic receptor but not in the mice lacking the M1 or M2 receptors, indicating that the airway remodeling effects of Ach are mostly dependent on M3 (145). During asthma, Ach also stimulates airway inflammation. It activates macrophages to release leukotriene B4, which in turn recruits eosinophils and neutrophils into the airways (146). The use of a long-lasting non-specific muscarinic antagonist, titropium, was able to inhibit eosinophilic inflammation (147). By contrast, M3-deficient mice showed similar levels of infiltrated eosinophils and T_h2 cytokine expression (145), suggesting that anti-inflammatory effects of blocking Ach might be mediated through a combination of muscarinic receptors.

The cellular sources of Ach in the lung might also be diverse. In addition to parasympathetic nerves, lung bronchial epithelial cells were shown to release Ach (148). While the contribution of neuronal and non-neuronal Ach in asthma is not yet completely understood, a recent study showed that the ablation of the parasympathetic nerve in the lungs by vagotomy decreased both AHR and inflammation in a canine model of asthma (149), indicating a key role for neuronal Ach in the physiopathology of asthma.

Sympathetic nerves that innervate the lung release noradrenaline (NA) that will act mostly on β2-adrenergic receptors (β2-ARs) on ASMCs to induce bronchodilation (Fig. 3B). Circulating adrenaline from other sympathetic fibers could also, in a similar way, induce bronchodilation. Indeed, β2-AR pharmacological agonists are the most effective bronchodilators for asthma and are commonly used to treat patients in combination with glucocorticoids to suppress inflammation (142, 150). The adrenergic system can be dysfunctional in allergic pathologies. In asthmatic patients, β2-ARs are desensitized in T cells leading to a decrease in NA-dependent inhibition of T-cell functions (151, 152). This desensitization is mediated by the thymus and activation-regulated chemokine (TARC) (153), which has been found to play a role in asthma (154, 155). Both parasympathetic and sympathetic neurons could contribute to regulate allergic immunity and inflammation in the respiratory tract.

Neuro-immune interactions in the gut and food allergies

In the GI tract, allergies take the form of reproducible adverse immune reactions to proteins present in food and the prevalence among adults can be as high 4% of the US population (156). The symptoms vary from diarrhea, nausea/vomiting and abdominal cramping to manifestations in the skin, in the cardio-respiratory tract and severe anaphylactic reactions that require hospitalization (156). Although the nervous system in the gut, including intrinsic ENS neurons and extrinsic neurons, is a complex system that has been the subject of many studies, our comprehension of its role in driving or inhibiting food allergies remains limited.

Interactions between mast cells and neurons in the gut

Mast cells, present in the submucosal tissues, play an important role in driving food allergies. Upon recognition of food allergens through specific IgE bound to cell-surface FCεR1, mast cells degranulate and release a number of pro-inflammatory mediators, such as histamine, eicosanoids or proteases. Beyond playing a major role in activating type 2 immune cells through their specific receptors, these mast cell mediators also act directly on enteric sensory neurons in the ENS.

A study showed that a cocktail of mediators released from stimulated human mast cells was able to induce activation of both human and guinea pig submucosal sensory neurons (157). Histamine, PGE2 and the leukotriene LTC4 are able to signal to naive and sensitized neurons. In submucosal neurons from guinea pigs sensitized by milk, stimulation with the food antigen β-lactoglobulin induced a depolarization that was similar to the one induced by the degranulation of mast cells (158, 159). Pharmacological inhibitors for the histamine receptor H2R, prostaglandin synthesis or for leukotriene synthesis were each able to partly reduce these neuronal responses to the antigen and to almost completely suppress neuronal responses when used in combination (159). At the same time, histamine inhibits the release of Ach or NA by acting on the inhibitory histamine receptor H3R present presynaptically on parasympathetic neurons (158) and on sympathetic neurons (159).

A recent paper showed that, in submucosal neurons from rats sensitized with chicken OVA, the main histamine receptor involved in the response was H1R, whereas H2R was present but played a minor role (160). Serine proteases (tryptase, chymase) are another type of mast cell mediator that can act directly on neurons. Proteases activate a family of related GPCRs called PARs, by cleaving a part of their extracellular domain, which in turn signals to activate the receptor. Myenteric sensory neurons and submucosal neurons from guinea pig small intestine are activated by tryptase and by specific agonists of the receptor PAR-2 (161, 162).

Neuropeptides in gut neuro-immune allergic interactions

Evidence for neurogenic inflammation was also found in the GI tract. Enteric mast cells from guinea pigs and from humans were found to express NK1 and the CGRP receptor by immunochemistry (163). Antidromic stimulation of spinal afferent neurons induces the release of the neuropeptides SP and CGRP in the small intestine of guinea pigs. These neuropeptides activate the degranulation of mast cells and the release of histamine and proteases, which in turn render the intrinsic ENS neurons more excitable (163).

In a model of food allergy induced by OVA, expression of CGRP mRNA was increased in the colon of mice while the distribution of nerve fibers remained unchanged, suggesting that CGRP release might be increased during food allergy (164). VIP is also released by intestinal IPANs and participates in GI smooth muscle relaxation (165). The receptors for VIP (VPAC1 and VPAC2) are also expressed on several immune cells types (ILC2s, macrophages, DCs, neutrophils), and VIP is known to play a role in neuro-immune interactions in pathologies such as colitis (16). However, the role of VIP in food allergies has not been studied. Therefore, as in the

lung and skin, neuropeptides could play an important role in neuronal signaling to the immune system and drive allergic reactions to food antigens.

Conclusions

Allergic inflammation in the skin, respiratory tract and the GI tract involves a complex cross-talk between neurons and immune cells that could play a critical role in mediating disease progression. Recent research into these neuro-immune interactions has brought new insights into mechanisms of action in allergic inflammation that go beyond classical roles for both the immune system and the nervous system. The immune system directly triggers sensory neuron activation through inflammatory mediators such as cytokines, histamine or neurotrophins. This immune-neuron communication mediates key physiological outcomes such as itch in AD, and cough and bronchoconstriction in asthma. Conversely, neurons directly communicate with immune cells through neurotransmitters including Ach and NA, or neuropeptides including CGRP, SP or VIP to directly modulate the development of type 2 inflammation.

Although immune-targeted treatments for allergic diseases have made important recent advances, patients with severe forms of asthma are often resistant to these treatments (166). Chronic itch and inflammation in AD is also often resistant to treatment (167). The nervous system could thus be a novel and exciting target for these conditions. Much work remains to discover the tissue-specific cellular and molecular neuro-immune mechanisms involved in allergies and the recent evidence gives hope of finding novel therapeutic targets in this new area of research.

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