



Sensory neurons control the functions of dendritic cells to guide allergic immunity

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Dendritic cells of the innate immune system and sensory neurons of the peripheral nervous system are embedded in barrier tissues and gather information about an organism's environment. While the mechanisms by which dendritic cells recognize and initiate adaptive immune responses to pathogens is well defined, how they sense allergens is poorly understood. Indeed, allergens induce dendritic cell maturation and migration *in vivo*, but not *in vitro*. How are adaptive immune responses to allergens initiated if dendritic cells do not directly sense allergens? Sensory neurons release neuropeptides within minutes of allergen exposure. Recent evidence demonstrated that while neuropeptides modify dendritic cell function during pathogen responses, they are required for dendritic cell function during allergic responses. These emerging studies suggest that sensory neurons do not just pass information along to the central nervous system, but also to dendritic cells, particularly during the initiation of adaptive immunity to allergens.

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Introduction

Dendritic cells (DCs) are innate immune cells strategically positioned in barrier tissues to detect the presence of pathogens. When DCs sense a pathogen, they carry this information to the draining lymph node where they instruct adaptive immune responses [1]. Functionally, DCs act as scouts, relaying information from the periphery to activate and differentiate adaptive immune cells in secondary lymphoid organs. While the process by which DCs recognize pathogens and initiate T helper (Th)1-biased and Th17-biased immune responses is well

defined, the method by which DCs perceive allergens is unknown.

Sensory neurons are specialized cells of the peripheral nervous system that provide information to an organism about its environment [2]. Much like DCs, sensory neurons extend dendrites into barrier tissues to monitor for changes and disturbances. Upon activation, sensory neurons relay signals to the central nervous system to withdraw from or stimulate the removal of noxious stimuli. Thus, sensory neurons are to the nervous system as DCs are to the immune system; both act as scouts and play essential 'relay' roles in their physiological systems. In both the skin and lung, DCs are closely associated with nerve fibers [3,4^{*,5}]. Given their similar physiological roles and spatial relationship, it was hypothesized that these cells collaborate in the allergic immune response. Here we review contemporary studies demonstrating sensory neuron-DC interactions, with a focus on the signaling pathways responsible for the development of adaptive immunity to allergens.

Structural recognition guides adaptive immunity to pathogens

Pathogens such as intracellular bacteria and viruses induce adaptive Type 1 immunity that is characterized by the generation of Th1 cells, while extracellular bacteria and fungi elicit Type 3 immunity that is defined by Th17 cells [1]. To generate the adaptive Th cell response, DCs sense pathogens in peripheral barrier tissues and then migrate to the draining lymph node where they instruct naïve T cell differentiation. In the periphery, immature DCs extend dendrites to continuously survey for the presence of pathogens, which are detected by pathogen-associated molecular patterns (PAMPs) binding to pattern recognition receptors (PRRs) [6]. PAMPs are structural motifs that are evolutionarily conserved across species and include the bacterial cell wall component lipopolysaccharide (LPS) that binds to the PRR toll-like receptor 4 (TLR4) [7] and α -mannans in fungal cell walls that are identified by the PRR Dectin-2 [8]. This method of sensing is called *structural recognition* because it relies on specific molecules that make up the fundamental architecture of a pathogen. When DCs identify a pathogen in their vicinity through their PRRs, an elegant process of maturation begins that is characterized by the contraction of their dendrites, upregulation of co-stimulatory molecules such as CD80 and CD86 [9], and transport of antigen-MHC Class II complexes to the plasma membrane [10,11]. At the same time,

chemokine receptors such as C-C chemokine receptor type 7 (CCR7) are upregulated [12]. Mature DCs expressing CCR7 respond to homeostatic levels of the C-C motif chemokine ligand 21 (CCL21), drawing them to the lymph node [12,13]. Once in the lymph node, mature DCs present antigen, provide co-stimulation, and release skewing factors that induce adaptive immunity by eliciting antigen-specific T cell differentiation [14]. These well-defined steps were established in the context of Type 1 and Type 3 immunity [1]. Although DCs are necessary for the initiation of Type 2 immune responses, the basic mechanisms by which DCs sense allergens is not clear [15].

Functional recognition guides adaptive immunity to allergens

Allergens, along with helminth parasites, typically evoke adaptive Type 2 immunity that is characterized by the generation of Th2 cells. Type 2 immunogens are incredibly varied and complex, lacking conserved and unique structures that could be broadly recognized by a limited number of DC-expressed PRRs [15]. Accordingly, the prototypical allergen papain readily induces the maturation and migration of DCs *in vivo*, but when applied to DCs *in vitro*, they fail to mature or migrate [4**]. Thus, DC sensing of Type 2 immunogens appears to be indirect. While allergens may not share structural features, many allergens share functional features such as protease activity or toxicity to membranes [15]. These functional activities of allergens are required for their immunogenicity; inhibiting the activities of allergens quenches their ability to induce innate immune activation and Th2 differentiation [16–18]. When tissues are injured through mechanical, chemical, or other insults, molecules and proteins called damage-associated molecular patterns (DAMPs) are released to alert innate immune cells to a threat to equilibrium [19]. Upon the first exposure to an allergen, DAMP release occurs within minutes to hours and includes cytokines such as interleukin-33 (IL-33), IL-25, and thymic stromal lymphopoietin (TSLP) [17,20,21*,22,23]. Protease allergens further process IL-33 into its mature form, enhancing signaling and increasing innate immune activation [21*]. Thus, it was proposed that allergens are sensed by *functional recognition*, a strategy relying on DAMP-induced DC maturation and migration. While mouse models demonstrated that DAMPs (IL-33 and TSLP) are required for allergen-induced Th2 differentiation, they are not sufficient [17,24–27]. Indeed, DCs treated with IL-33 upregulate the co-stimulatory molecules CD80 and CD86 and the antigen-presenting molecule MHC Class II [25,28]. However, mice lacking the IL-33 receptor ST2 exhibit intact DC migration in response to allergen, indicating that an additional signal is required for allergen-induced DC migration and the induction of Th2 differentiation [25]. This requirement for an additional signal is underlined by the observation that DAMPs like IL-33 are involved in sterile tissue

repair pathways [19]. It thus follows that DCs would require an additional signal to fully license them to initiate an adaptive immune response, rather than antigen-independent tissue repair.

Allergens activate sensory neurons and induce neuropeptide release

Allergic diseases are defined by inappropriate immune responses against otherwise harmless antigens, termed allergens. The physiologic function of this response was largely thought to be anti-helminth until 1991 when Margie Profet introduced the toxin hypothesis of allergy [29]. The toxin hypothesis states that all allergens are toxins themselves, or commonly associated with toxins, and that adaptive Type 2 immune responses against allergens/toxins are protective, not detrimental. Experimental evidence for this theory was provided when it was found that the toxic venom of honeybees, a robust allergen, induces adaptive Type 2 immunity that protects against a secondary, potentially lethal exposure [17,30]. This is compelling evidence that the toxin hypothesis of allergy applies to common allergens. In the search for a cellular sensor of allergens upstream of DCs, it was thus necessary to view allergens as toxins.

Analogous to DCs transmitting antigenic information, sensory neurons relay signals from the periphery to the central nervous system. Toxins derived from a variety of animals, including those of spiders and snakes, rapidly activate sensory neurons and induce the unpleasant sensation of pain [31,32]. This leads to withdrawal from and avoidance of that toxin, similar to the conditioned aversion allergic animals exhibit against their sensitized allergens [33]. If allergens are viewed as toxins, it is natural to imagine that sensory neurons may be early targets of allergens. Within seconds to minutes, activated sensory neurons can release neuropeptides from pre-formed granules that signal to local immune cells. For example, neurons harvested from the dorsal root ganglia (DRG), where the cell bodies of sensory neurons are housed, rapidly release the neuropeptide calcitonin gene-related peptide (CGRP) when stimulated with live bacteria or bacterial *N*-formylated peptides, pore-forming toxins, or the hemolytic exotoxin streptolysin S [34,35]. During infection, CGRP suppresses the immune response, indicating that neuropeptides derived from sensory neurons can modulate immune function [34,35,36*].

Neuropeptides control the maturation, migration, and cytokine production of DCs

A precise, choreographed sequence of events marks the maturation of immature DCs into antigen-bearing cells prepared to induce naïve T cell differentiation. Upon pathogen recognition, immature DCs: (1) increase the expression of co-stimulatory molecules and MHC Class II for antigen presentation [9–11], (2) upregulate chemokine receptors and migrate to the secondary lymphoid organs

[12,13], and (3) provide skewing cytokine signals that dictate Th cell differentiation [14]. At each of these steps, recent evidence suggests that neuropeptides work in an activating or regulatory capacity to tailor the development of antigen-specific immunity.

Bone-marrow derived (BM) DCs were used in a number of studies to model how neuropeptides influence DC maturation. Substance P (SP), vasoactive intestinal peptide (VIP), and pituitary adenylate cyclase-activating peptide (PACAP) increased the expression of co-stimulatory molecules in immature BMDCs [37,38,39^{*}]. Thus, neuropeptides can induce features of DC maturation even in the absence of PRR-induced maturation. In contrast, the induction of co-stimulatory molecules in BMDCs matured with LPS was inhibited by VIP and PACAP, indicating that these neuropeptides have context-specific control of DC maturation [38]. A similar inhibitory effect was seen in BMDCs matured with LPS and treated with CGRP, indicating that neuropeptides may directly and indirectly control DC maturation [40].

The migration of DCs to secondary lymphoid organs is enabled during maturation through the upregulation of chemokine receptors such as CCR7. In BMDCs, PACAP increased the expression of *Ccr7*, indicating that this neuropeptide might control the homing of DCs to the lymph node [39^{*}]. Indeed, in a mouse model of contact hypersensitivity, PACAP inhibition decreased the migration of DCs to the draining lymph node [39^{*}]. Interestingly, pulmonary DCs dose-dependently migrated towards SP [41]. A similar study found that SP enhanced, while CGRP and VIP inhibited, the chemotaxis of immature DCs to a prion antigen [42]. These data suggest that neuropeptides may act as chemokine-like molecules in some instances, while in others tuning the migration of DCs that is elicited by other triggers.

When mature DCs arrive to the lymph node to induce adaptive immunity, they produce skewing signals that bias naïve T cell differentiation. A role for neuropeptides in the production of skewing signals was implied when an early study discovered that VIP and PACAP inhibited CXCL10 and enhanced CCL21 in BMDCs matured with LPS [43]. This concept was established when it was later found that CGRP impaired the production of IL-12, TNF α , and IL-6 in BMDCs matured with LPS [44,45]. Concurrently, maturing DCs treated with CGRP enhanced their production of IL-10, adopting a tolerogenic phenotype [45]. VIP produced similar results in maturing DCs, in that the production of IL-12 and TNF α was reduced, while the release of IL-10 was heightened [46]. Regulation of DC cytokine production by the neuropeptides CGRP and VIP had a profound impact on T cell differentiation. Indeed, CGRP dose-dependently impaired antigen-specific T cell proliferation [40]. When

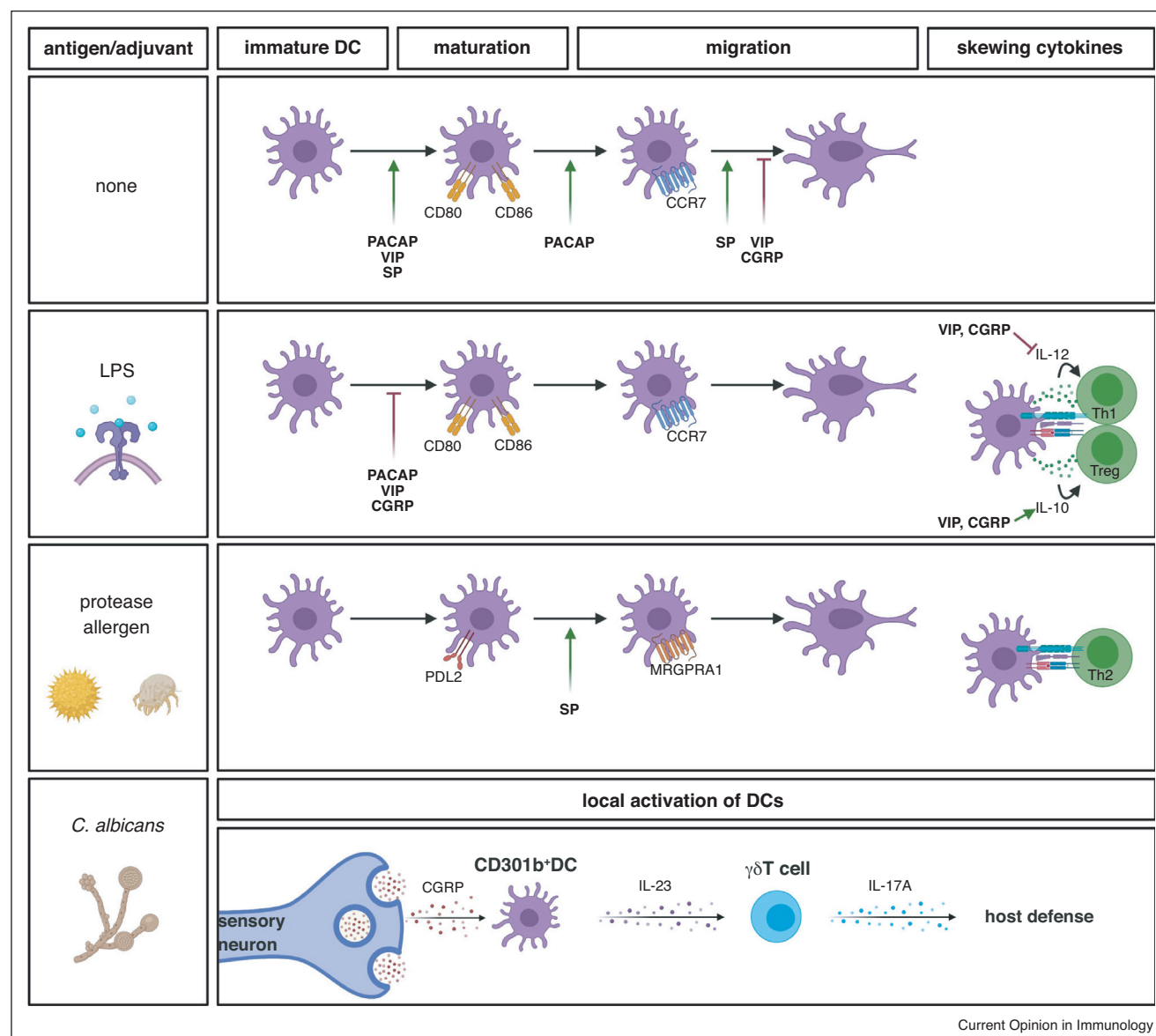
naïve T cells were co-cultured with DCs treated with CGRP, the generation of CD4⁺IFN γ ⁺ T cells was reduced [45]. Similar studies using VIP-treated DCs found that co-culture with naïve T cells prevented the generation of IFN γ , while inducing the formation of IL-10 and TGF β , secreting T cells [46,47]. These studies suggest that neuropeptides impact adaptive T cell differentiation by altering the production of skewing cytokines derived from DCs.

The referenced studies provide an initial, albeit incomplete, framework that neuropeptides control the movements and functions of DCs during a primary immune response (Figure 1). Within this framework emerge general themes such that SP and PACAP represent DC-activating neuropeptides and CGRP and VIP represent DC-regulatory neuropeptides. And yet, inconsistencies in this basic assessment argue for a more nuanced approach. Indeed, CGRP derived from sensory neurons in the skin induces IL-23 in dermal DCs, promoting IL-17 release from $\gamma\delta$ T cells and local inflammation [5,48]. It is unclear whether these conflicting observations are the result of DC heterogeneity or whether they suggest that neuropeptides may play different roles in the context of different immunologic stimuli.

Neuropeptides license DCs to induce adaptive Type 2 immunity to allergens

The observation that DCs respond *in vivo*, but not *in vitro* to protease allergen exposure, suggested the presence of an alternate primary sensor of allergens. A clue to this identity came from Serhan *et al.* who found that nociceptors, the sensory neurons responsible for the sensation of pain, were potently activated by the cysteine protease activity of house dust mite (HDM) allergen [49^{••}]. Nociceptors treated with HDM released SP, activating mast cells through their expression of MRGPRB2 and producing a local inflammatory response. Likewise, we found that cysteine and serine protease allergens directly activated sensory neurons *in vivo* and *in vitro*, leading to neuronal calcium flux, SP release, and the sensation of itch. At the same time, protease allergens inhibited the release of CGRP from DRG neurons in culture as well as from flank skin explants arguing that biased SP release played a potential role in the response to allergens in naïve mice [4^{••}]. Nav1.8⁺ nociceptive neurons in the skin were found in close apposition to CD301b⁺ DCs, the subset that is required for Th2-skewing [50], arguing that nociceptive neurons might relay allergen detection to DCs through SP release. Indeed, CD301b⁺ DCs expressed the SP receptor MRGPRA1 and upon allergen immunization their migration to the lymph node was dependent on SP and their expression of MRGPRA1 [4^{••}]. SP directly induced CD301b⁺ DC migration to the draining lymph node and Th2 differentiation was impaired when this signaling pathway was blocked. However, SP did not lead to the upregulation of classical

Figure 1



Neuropeptide control of dendritic cell (DC) maturation, migration, and biased T cell differentiation.

Immature DCs are antigen naïve cells that act as detectives in barrier tissues, investigating for the presence of threats to an organism, particularly pathogens. Even in this immature state, neuropeptides including PACAP, VIP, and SP can generate a mature phenotype through the upregulation of the co-stimulatory molecules CD80 and CD86 upregulation. Similarly, PACAP induces *Ccr7* in immature DCs, while SP enhances and VIP or CGRP inhibits, the migration of immature DCs to an antigen. LPS, a canonical PAMP, induces DC maturation, migration, and licenses them to initiate T cell differentiation through the production of skewing cytokines. PACAP, VIP, and CGRP inhibit LPS-induced CD80 and CD86. In addition, VIP and CGRP inhibit the production of IL-12 in LPS-matured DCs, while enhancing the production of IL-10. Together, these changes prevent the differentiation of IFN γ -producing T cells and augment the production of IL-10-secreting T cells. During the allergic immune response, sensory neurons release SP that causes DC migration through the expression of the MRGPRA1 receptor. In the skin, the pathogenic yeast *C. albicans* elicits the release of CGRP from sensory neurons that acts on local CD301b⁺ DCs to release IL-23, activating $\gamma\delta$ T cells to produce IL-17A.

costimulatory molecules on DCs *in vitro* and SP-induced CD301b⁺ DC migration was unable to evoke Th2 differentiation on its own [4•]. Together, these data suggest that the initiation of Type 2 immunity requires non-redundant signaling from neuropeptides and alarmins.

Conclusions and perspectives

In the canonical immune response to a pathogen, DCs mature, migrate to secondary lymphoid organs, and induce T cell differentiation. The presence of activating or regulatory neuropeptides at each of these carefully

coordinated steps determines the extent of DC activation. The data suggest that neuropeptides modify DC activation in the context of PRR signaling, altering DC function much like inflammasome-derived IL-1 β induces a state of hyperactivation in DCs matured with LPS [51]. Conversely, in the Type 2 immune response to allergens neuropeptides do not just modify, but are a signal that is *required* for DCs to be able to initiate adaptive Type 2 immunity to allergens. DCs must rely on neuropeptide signals from sensory neurons because they cannot directly sense the presence of allergen activity through PRRs. In this pathway, sensory neurons act as scouts, perceiving the activity of allergens and relaying this information to adjacent DCs through the release of neuropeptides. An open question is whether or not the channels of communication between sensory neurons and DCs occur constitutively and bidirectionally. That is to say, can the information that each cell gathers as a result of their scouting operations in barrier tissues be easily passed between each other? Could these interactions also occur in lymphoid tissues, as was suggested by a recent study identifying peptidergic sensory neuron innervation in lymph nodes [52]? Given the requirement of DAMPs in the initiation of adaptive immunity to allergens [17,24–27], we speculate that activating neuropeptides must signal together with DAMPs to authorize DCs to initiate adaptive Type 2 immunity [53]. Following the initiation of the adaptive immune response to allergens, emerging evidence suggests that neuropeptides may continue to modify the course of chronic allergic inflammation. Recent studies found that CGRP constrained allergic inflammation in a model of food allergy [54], while nociceptors were required for allergic airway inflammation in sensitized and challenged mice, likely through substance P [55]. While not a bona fide neuropeptide, the neurotrophic factor neuritin was expressed by follicular Tregs and controlled IgE production by B cells, suggesting that it may be a central mechanism in the development and chronicity of allergic diseases [56]. While our experimental understanding of sensory neuron-DC interactions in the immune response is still in its infancy, neuropeptides are nevertheless exciting targets of novel therapeutics for the treatment of allergic diseases.

Conflict of interest statement

Caroline Sokol is a paid consultant for Bayer and Merck and receives sponsored research support from GSK.

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