

Sensory neurons drive adaptive immunity in contact hypersensitivity

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In this issue of the *Journal of Allergy and Clinical Immunology*, Yamamoto et al¹ provide new insights into the induction of adaptive immunity and its control by nociceptive sensory neurons. The authors demonstrate that the presence of a contact allergen stimulates sensory nerves to release the neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP), promoting dendritic cell (DC) migration to lymph nodes for efficient T-cell priming.

The skin is exposed to a variety of environmental insults. Sensory nerves of the skin respond to environmental triggers, including touch, pressure, temperature, pain, and itch. The resulting afferent signals allow us to identify harmful stimuli and generate protective behavior. Stimulus-specific somatosensory neurons transmit these signals from the skin to the dorsal root ganglia. The signals then ascend to the brain via the spinal cord and cause a respective perception.²

The modulation of skin immune functions by neuropeptides was initially proposed by case studies. These reports suggested that complex inflammatory skin disorders such as psoriasis improve following damage or transection of nerves that innervate the affected skin sites.³ Subsequent mouse studies provided sound evidence that sensory neurons indeed control immune responses in skin. In one of the pivotal studies, Riolo-Blanco et al investigated the induction of psoriasis-like dermatitis by imiquimod. Their work showed that production of IL-23 by DCs and induction of skin inflammation relied on imiquimod-activating TRPV1⁺ sensory neurons.⁴ Kashem et al⁵ showed that TRPV1⁺ nociceptors are directly stimulated by the fungal commensal-pathogen *Candida albicans*. Dermal DCs that were found in close proximity to these sensory neurons were then activated by CGRP to orchestrate an IL-23-dependent IL-17-driven anti-*Candida* response.⁵ In their subsequent work, the same group showed that optogenetic TRPV1⁺ neuron activation was sufficient to induce type 17 inflammation. Interestingly, they found that a nerve reflex arc mounted an anticipatory immune response in neighboring skin that was sufficient to control *Candida* infection.⁶ Other examples of neuronal regulation of cutaneous immunity are studies in which protease-active house dust mite allergen and *Staphylococcus aureus* triggered neurotransmitter release by

sensory neurons to modulate local immune responses.⁷ Beyond skin, Huang et al recently demonstrated that bidirectional neuro-immune crosstalk is also active in lymph nodes. Their work showed that inflammatory signals act on sensory neurons, which in turn modulate gene expression in endothelial, stromal, and innate immune cells.⁸

Yamamoto et al investigated the immunoregulatory functions of the neurosensory system of the skin during induction of a primary T-cell-dependent immune response.¹ They made use of the contact hypersensitivity (CHS) reaction. Contact allergens are a diverse group of chemicals that are well known for their inherent ability to induce a “sterile” innate inflammatory response by activating different signaling pathways. The CHS reaction in mice is a basic model for studying the induction of an adaptive immune response within skin. During the sensitization phase, contact allergens applied to skin are taken up by DCs, which then become activated and eventually migrate to the regional lymph nodes. There, they present the antigen and induce a T-cell-dependent primary immune response. Subsequently, allergen-specific T cells are distributed to the skin, and following reexposure of sensitized animals with the contact allergen, they mount an inflammatory skin reaction.

Yamamoto et al¹ begin their studies by showing that both surgical denervation of the skin and resiniferatoxin-induced chemical ablation of TRPV1⁺ nociceptors before sensitization suppress the CHS response, thereby confirming previous findings.⁹ The authors used the contact allergen oxazolone. Although contact allergens differ in their chemical structure and their inherent way of inducing a sterile inflammatory response, the authors obtained similar results with the contact allergens dinitrofluorobenzene and fluorescein isothiocyanate.

While asking how denervation caused an attenuated CHS response, Yamamoto et al.¹ made the central observation that DCs, which normally migrate to lymph nodes, are retained in the allergen-challenged but denervated skin. The authors then screened the dorsal root ganglia of denervated and control mice for changes in their levels of expression of neuropeptides and growth factors. They found that the levels of PACAP and substance P were significantly decreased in denervated mice. Administration of PACAP, but not substance P, was then identified as rescuing DC migration to lymph nodes in denervated skin and allowing for a proper CHS response. Consistently, applying a PACAP receptor antagonist resulted in a reduced CHS response in nondenervated mice that was comparable to the CHS response in denervated mice. In the search for a mechanism by which PACAP promoted the CHS response, the authors found a PACAP-dependent upregulation of the costimulatory molecules CD80 and CD86 on DCs and, more importantly, upregulation of CCR7 and CXCR4 (Fig 1). Accordingly, they observed increased migration of PACAP-treated DCs toward the CCR7 ligand CCL21 and the CXCR4 ligand CCL12.

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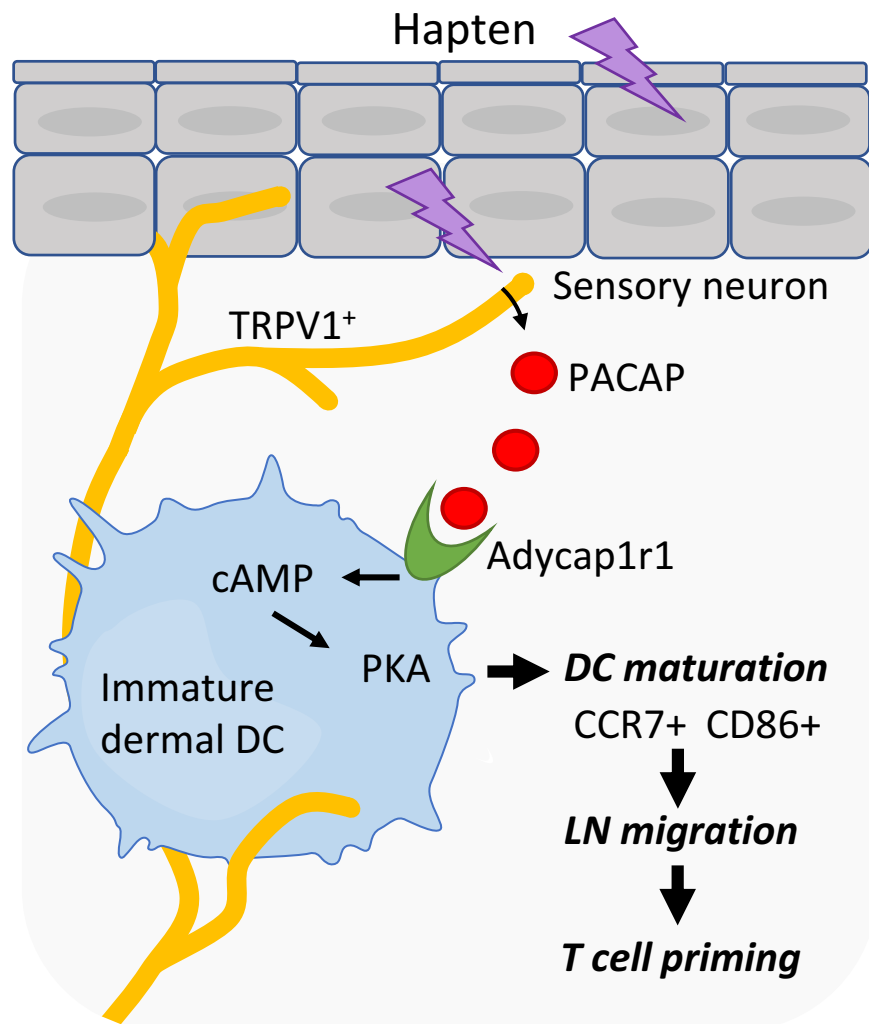


FIG 1. Model representation of sensory neurons driving adaptive immunity in contact allergy. Haptens stimulate cutaneous TRPV1⁺ sensory nerves to release PACAP. PACAP binds to its receptor Adycap1r1 on nerve-associated dermal DCs, inducing DC maturation. DCs migrate to regional lymph nodes (LNs) and efficiently prime hapten-specific T cells. As a result of this neuroimmune crosstalk, inflammation during the elicitation phase is increased. *cAMP*, Cyclic adenosine monophosphate; *PKA*, protein kinase A.

In the next piece of the puzzle, Yamamoto et al¹ investigated which of the 2 PACAP receptors, Adycap1r1 or Vipr2, is responsible for mediating the observed effects on DCs. Here, the authors demonstrated that increased mRNA expression levels of CCR7 and CXCR4 after PACAP treatment was reproduced in Vipr2-knockdown bone marrow–derived DCs (BMDCs) but not in Adycap1r1-knockdown BMDCs. This suggested that Adycap1r1 is the PACAP receptor on DCs that mediates the observed modulation of DC functions.

To finally show *in vivo* that the PACAP-mediated effects on DCs during sensitization are necessary to initiate a proper CHS response, the authors reconstituted DC-depleted CD11c-DTR mice with Adycap1r1-knockdown or control BMDCs. Although providing control BMDCs led to a normal CHS response, reconstitution with Adycap1r1-knockdown BMDCs did not. With these *in vivo* results the authors clearly established that in contact allergen–challenged skin sensory neurons provide a ticket for DCs to migrate to the lymph nodes and initiate a primary immune response (Fig 1).

By showing how nociceptive sensory neurons can drive adaptive immunity, the study by Yamamoto et al¹ significantly contributes to our understanding of neuroimmune communication within skin. It appears relevant to note that with regard to sensory neurons of the skin, the same stimulus may cause a multilayered response. Single-cell analysis of dorsal root ganglia led to the classification of 2 peptidergic and 3 nonpeptidergic sensory neurons with preferential and overlapping expression of cation channels, G-protein–coupled receptors, and receptors for cytokine signaling.² Whereas Yamamoto et al¹ show stimulatory effects of TRPV1⁺ (NP3) sensory neurons after exposure to a contact allergen, Zhang et al¹⁰ recently demonstrated that stimulation of Mrgpr⁺ sensory neurons (NP1) by contact allergens attenuated inflammation by blocking mast cell activation. Interestingly, Mrgpr⁺ neurons are reduced in the absence of Langerhans cells (LCs). This may explain previous results showing increased CHS reactions in mice with long-term depletion of LCs. In fact, the regulatory role of LCs and the stimulatory role of dermal DCs in CHS may be partially

explained by their differential interplay with different types of sensory neurons.

Seminal advances in our understanding of neuroimmune communication within skin have recently been made. Yamamoto et al¹ contribute to this understanding by demonstrating that sensory neurons can directly promote the acquisition of adaptive immunity through stimulation of DC functions (Fig 1).

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REFERENCES

1. Yamamoto Y, Otsuka A, Ishida Y, Wong LS, Seidel JA, Nonomura Y, et al. Pituitary adenylate cyclase-activating polypeptide promotes cutaneous dendritic cell functions in contact hypersensitivity. *J Allergy Clin Immunol* 2021;148:xxx-xxx.
2. Tamari M, Ver Heul AM, Kim BS. Immunosensation: neuroimmune cross talk in the skin. *Annu Rev Immunol* 2021;39:369-93.
3. Joseph T, Kurian J, Warwick DJ, Friedmann PS. Unilateral remission of psoriasis following traumatic nerve palsy. *Br J Dermatol* 2005;152:185-6.
4. Riol-Blanco L, Ordovas-Montanes J, Perro M, Naval E, Thiriot A, Alvarez D, et al. Nociceptive sensory neurons drive interleukin-23-mediated psoriasiform skin inflammation. *Nature* 2014;510:157-61.
5. Kashem SW, Riedl MS, Yao C, Honda CN, Vulchanova L, Kaplan DH. Nociceptive sensory fibers drive interleukin-23 production from CD301b+ dermal dendritic cells and drive protective cutaneous immunity. *Immunity* 2015;43:515-26.
6. Cohen JA, Edwards TN, Liu AW, Hirai T, Jones MR, Wu J, et al. Cutaneous TRPV1(+) neurons trigger protective innate type 17 anticipatory immunity. *Cell* 2019;178:919-32.e14.
7. Chiu IM, Heesters BA, Ghasemlou N, Von Hehn CA, Zhao F, Tran J, et al. Bacteria activate sensory neurons that modulate pain and inflammation. *Nature* 2013;501:52-7.
8. Huang S, Ziegler CGK, Austin J, Mannoun N, Vukovic M, Ordovas-Montanes J, et al. Lymph nodes are innervated by a unique population of sensory neurons with immunomodulatory potential. *Cell* 2021;184:441-59.e25.
9. Beresford L, Orange O, Bell EB, Miyan JA. Nerve fibres are required to evoke a contact sensitivity response in mice. *Immunology* 2004;111:118-25.
10. Zhang S, Edwards TN, Chaudhri VK, Wu J, Cohen JA, Hirai T, et al. Nonpeptidergic neurons suppress mast cells via glutamate to maintain skin homeostasis. *Cell* 2021;184:2151-66.e16.