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1 Bidirectional sensory neuron-immune interactions: a new
2 vision in the understanding of allergic inflammation.

3

4 Short title: Nociception, sensory neurons and hypersensitivity

5

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7

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36 **Abstract**

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

47

48

49 **Introduction**

50 Nociception is the sensing of noxious chemical, mechanical, or thermal stimuli. First
51 introduced by Sherrington in 1900 in the context of pain perception [1], nociception allows
52 animals to rapidly sense and avoid environmental hazards including piercing objects, burning
53 heat, and freezing temperatures [2]. The immune system provides an additional layer of
54 protection in the event that prevention of invasion by pathogens is breached even with optimal
55 sensing and behavioral avoidance of environmental threats. Allergy (i.e., hypersensitivity) is a
56 pathologic inflammatory and, subsequent neurosensory, process that is triggered by
57 exaggerated responses to otherwise harmless environmental substances.

58

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

70

71 **Unraveling the identity of sensory neurons**

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

79

80 Most nociceptors and pruriceptors are small diameter unmyelinated C fibers [9]. In
81 development, C fiber neurons initially appear as one population characterized by expression
82 of the nerve growth factor receptor TrkA. However, later in development they diverge into

83 two subpopulations, one that maintains TrkA expression, and the other that downregulates
84 expression of TrkA [10] while upregulating the common glial-derived neurotrophic factor
85 family ligand receptor Ret that is selectively labeled by isolectin B4 (IB4) [11]. TrkA-
86 expressing nerve fibers also express neuropeptides like substance P (SP) and calcitonin-gene
87 related peptide (CGRP), and are thus referred to as peptidergic (PEP) neurons. In contrast,
88 IB4-positive nerve fibers generally do not express SP or CGRP during development period
89 and are thus considered nonpeptidergic (NP) [9,12–14]. However, emerging studies using
90 unbiased single-cell RNA sequencing (scRNA-seq) of murine DRG neurons have revealed
91 that some NP neuron clusters also contain markers for PEP neurons (i.e., CGRP gene *Calca*)
92 [15,16]. Therefore, it is likely that neurons traditionally considered NP have the capability of
93 releasing neuropeptides as well. Thus, a major area of future inquiry will be in understanding
94 the precise identity of individual neurons that are specialized to encode specific sensations,
95 release distinct neuropeptides, or perform both functions to shape tissue immunity and
96 inflammation.

97

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

106

107 **Neurons as sensors of immune stimuli**

108 There is increasing recognition that nociception is modulated by the immune system. A
109 variety of tissue-resident cells like mast cells (MCs) and macrophages/microglia have been
110 implicated in nociception via their production of cytokines and granule-associated mediators
111 [20,21]. Meningeal mast cell and sensory neuron bi-directional interactions for instance, play
112 fundamental roles in migraine pathophysiology, resulting in the sensitization of trigeminal
113 nociceptors [22]. IL-1 β and TNF- α are two of the first cytokines shown to act directly on the
114 nervous system in the context of pain [23–27]. Both IL-1 β and TNF- α -induced neuronal
115 excitability is dependent on p38-MAPK downstream signaling and the activation of ion
116 channels like TRPV1 [25,28,29]. Other cytokines such as IL-6 and IL-17A have also been

117 identified to promote pain in joint inflammation models [30,31]. In contrast, the anti-
118 inflammatory cytokine IL-10 has been shown to attenuate pain responses recently [32]. Taken
119 together, it appears that the sensory nervous system can both sense stimuli that promote
120 noxious signals or even be modulated to suppress nociception. However, how such
121 neuroimmune biology translates across the variety of sensory neurons innervating different
122 organs remains a vibrant area of exploration [33,34].

123

124 In addition, a number of cytokines that are upregulated in allergy have the capability to act on
125 pruriceptors. In 2013, Wilson *et al.* found that, the epithelial cell-derived cytokine thymic
126 stromal lymphopoietin (TSLP) promotes itch by stimulating itch-sensory neurons [35]. Later
127 in 2014, IL-31 was shown to activate pruriceptors and thus, is the first type 2 immunity-
128 associated cytokine to function as a pruritogen [36]. In 2017, Oetjen *et al.* identified that IL-
129 4R α , the receptor for the canonical type 2 effector cytokines IL-4 and IL-13, is expressed by
130 itch-sensory neurons and depend on downstream Janus kinase (JAK) signaling to promote
131 neural hypersensitivity [37]. Indeed, blockade of TSLP, IL-31, IL-4R α , IL-13, and JAK are
132 either approved or currently in clinical trials for the treatment of atopic dermatitis (AD) and/or
133 other chronic itch disorders (**Table 1**) [38–50]. Collectively, these basic and translational
134 advances illustrate how, in addition to external environmental stimuli, sensory neurons can
135 respond to endogenous cytokine signals to elicit, enhance, and even suppress pain and itch in
136 tissues.

137

138

139 **Role of sensory neurons in the regulation of allergic skin diseases**

140 AD is a frequent chronic inflammatory skin disease with strong impact on health-related
141 quality of life, especially due to itch burden [51]. It was generally thought that pruriceptors
142 were involved in manifestations of type 2 (allergic) skin diseases, such as AD, mainly by
143 promoting itch-induced scratching behavior. Recently, a new role was uncovered by Serhan,
144 Basso *et al.* for SP-producing sensory neurons in regulating Mrgprb2⁺ MC activation and
145 subsequent development of type 2 skin inflammation [52] (**Figure 1A**). The authors
146 demonstrated that, compared with wild type (WT) mice, mice depleted in TRPV1⁺ sensory
147 neurons, *Tac1*^{-/-} mice (that lack SP), MC-deficient mice and *Mrgprb2*^{-/-} mice, were protected
148 from the development of pathogenic type 2 inflammation and associated skin lesions. They
149 then showed that common domestic allergens with cysteine protease activity, e.g. house dust
150 mites (HDMs), could directly activate TRPV1⁺ neurons to release SP. Using a new intravital

151 imaging method, they showed that a large proportion of projections from activated TRPV1⁺
152 nociceptors formed physical contacts with MCs, and that penetration into the dermis of
153 HDMs led to the sequential activation of nociceptors and adjacent MCs (**Figure 1A**). This
154 study strongly suggests that TRPV1⁺ *Tac1*⁺ nociceptors and Mrgprb2⁺ MCs form “sensory
155 clusters” capable of detecting the presence of allergenic alarms and initiating the development
156 of pathogenic type 2 immune responses in the skin [52]. Based on these results, it would be
157 interesting to consider an updated version of the etiology of AD by focusing on neuro-
158 immune crosstalk prior to the development of pathogenic type 2 immunity.

159

160 The communication between sensory neurons and MCs is in fact bidirectional. In a recent
161 article [53], Meixiong *et al.* used intravital calcium imaging to examine sensory neurons
162 activation in the context of non-histaminergic itch. While canonical IgE/FcεRI-mediated MC
163 activation in the skin mainly triggered the activation of histamine (and capsaicin)-sensitive
164 H_{1,4}R⁺ sensory neurons, Mrgprb2-mediated MC activation resulted in the broad excitation of
165 Mrgprd⁺, Mrgpra3⁺, and 5ht1f⁺ sensory neurons, three subpopulations of well-defined NP
166 pruriceptors [15]. Such difference in the activation of neuronal subsets resulted, at least in
167 part, from a differential release of MC granule-associated pruritogens: high proportion of
168 histamine and serotonin via FcεRI, and of tryptase (and maybe other proteases) via Mrgprb2
169 (**Figure 1A**). It is generally thought that skin MCs would be primarily involved in
170 histaminergic itch. However, many chronic itch conditions are refractory to histamine
171 antagonists, including AD and allergic contact dermatitis (ACD). Interestingly, the PAMP1-
172 20 neuropeptide is upregulated in skin lesion of patients with ACD and is a well-known
173 agonist of Mrgprb2/X2. In line with these data, using three separate models of allergic skin
174 inflammation, Meixiong *et al.* reported that *Mrgprb2*^{-/-} animals exhibited significantly less
175 itch compared with WT mice [53]. Consequently, it is very tempting to speculate that
176 PAMP1-20-mediated MRGPRX2 activation is a major mechanism of MC-dependent non-
177 histaminergic itch in patients with ACD.

178 In addition to differential pathways by which MCs trigger histaminergic and non-
179 histaminergic itch, respectively, Wang *et al.* recently identified that AD-associated
180 inflammation activates basophils in the blood. Upon sensitization to allergen, in this context,
181 basophils are prone to enhance their ability to respond to IgE, resulting in a distinct basophil-
182 sensory neuronal itch axis that is linked by the production of leukotriene C4 from basophils
183 [54]. Thus, basophils are capable of overriding the histaminergic processes triggered by MCs
184 to elicit other distinct itch pathways.

185

186 **Emerging role of sensory neurons in allergic lung inflammation**

187 Wallrapp A *et al.* reported an interaction between type 2 innate lymphoid cells (ILC2s) and
188 neuromedin U (NMU)⁺ neurons, in models of allergic lungs inflammation [55]. The authors
189 profiled mouse lung-resident ILCs using scRNAseq and found that the neuropeptide receptor
190 *Nmur1* was preferentially expressed by ILC2s at steady state and after IL-25 stimulation.
191 NMU, the ligand of NMUR1, activated ILC2s *in vitro*, and *in vivo* co-administration of NMU
192 with IL-25 strongly amplified allergic inflammation (**Figure 1B**). Loss of NMU-NMUR1
193 signaling reduced ILC2 frequency and effector function, and altered transcriptional programs
194 following HDM challenge *in vivo*.

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

215

216 **Future perspectives**

217 Various reports have now demonstrated that bidirectional dialogues between sensory neurons
218 and immune cells can impact on the development of frequent allergic skin and lungs

219 disorders. In addition, three studies have suggested that intrinsic primary afferent neurons [65]
220 and neuroimmune interactions [66,67] in the intestine could also contribute to the
221 pathophysiology of food allergy. Production of the neuritin protein, that targets B cells, by
222 follicular regulatory T cells has also recently emerged as a potential mechanism to suppress
223 IgE-mediated allergies by limiting IgE class switch recombination [68]. Finally, three recent
224 reports also opened new very promising areas of investigation by showing that lymph nodes
225 were innervated by a unique subset of sensory neurons that might regulate local gene
226 expression [69], that the innate immune regulator STING, a sensor of self- and pathogen-
227 derived DNA could control nociception via type I interferon signaling [70] and finally that
228 nociceptors could directly influence the mobilization of haematopoietic stem cells in the bone
229 marrow [71]. While much remain to be done to understand how nociception and sensory
230 neurons regulate human allergic disorders, the development of next-generation therapeutics
231 specifically targeting neuroimmune crosstalk is an exciting area of exploration for the future.

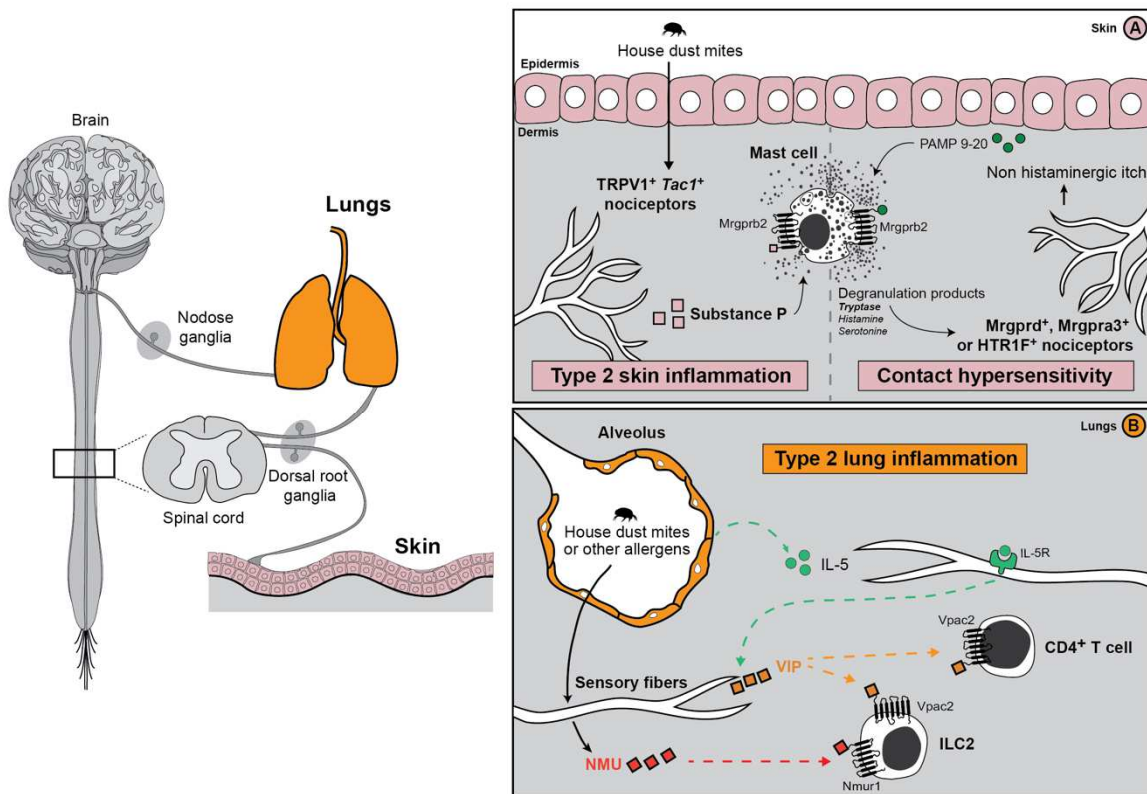
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235 **Figures and table**

236



237

238 **Figure 1. Neuroimmune interactions play a crucial role in models of allergic skin and**

239 **lungs disorders.** (A) Widely distributed domestic allergens can directly activate

240 TRPV1⁺Tac1⁺ nociceptor-MrgprB2⁺ MC sensory clusters to drive the development of type 2

241 skin inflammation [52]. MC activation through the receptor MrgprB2 also contributes to non-

242 histaminergic itch [53]. As compared to IgE-FcεRI signaling, MrgprB2-activated mast cells

243 released more tryptase (but less histamine and serotonin) and excited distinct itch-sensory

244 neuron populations expressing Mrgprd, Mrgpra3, or HTR1F. (B) The secretion of IL-5 in

245 response to the penetration of allergens in the lungs activates IL-5 receptor on nociceptors that

246 in turn release the neuropeptide vasoactive intestinal peptide (VIP) [57]. Allergens also

247 stimulate sensory neurons to release neuromedin U (NMU). Such neuropeptides activate

248 innate lymphoid cell 2 (ILC2) through VIP receptor 2 (VPAC-2) and NMU receptor 1

249 (NMUR1), and favor the development type 2 lung inflammation [55].

250

251

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 Abrocitinib Upadacitinib Ruxolitinib Cream Delgocitinib Ointment	Inhibitors	[38–40,43,44]

252 **Table 1. Innovated Therapeutic Approaches for Atopic Dermatitis.** Abbreviations: JAK,
 253 Janus kinase; NCT, National Clinical Trial; mAb, monoclonal antibody; TSLP, thymic
 254 stromal lymphopoietin.

255

256

257 **Author contributions**

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

259

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264

265 **Conflict of interest statement:**

266 N.G. is acting as Chief Scientific Officer consultant for Genoskin. He is a member of the
 267 scientific advisory board for MaxiVAX. He has served as consultant for Boehringer
 268 Ingelheim, GlaxoSmithKline, Escient Pharmaceuticals and Novartis. He has a patent pending
 269 for the treatment of type 2 inflammation and mast cell-dependent disorders. B.S.K. has served

270 as a consultant for AbbVie, ABRAX Japan, Almirall, AstraZeneca, Cara Therapeutics,
271 Daewoong Pharmaceutical, Incyte Corporation, LEO Pharma, Lilly, Maruho, Menlo
272 Therapeutics, OM Pharma, Pfizer, and Third Rock Ventures. He has also participated on the
273 advisory board for Almirall, Boehringer Ingelheim, Cara Therapeutics, Kiniksa
274 Pharmaceuticals, Menlo Therapeutics, Regeneron Pharmaceuticals, Sanofi Genzyme, and
275 Trevi Therapeutics. He is stockholder of Locus Biosciences. M.T. has served as consultant or
276 speaker for Sanofi Genzyme and F.W. declare no competing interests.

277

278 **References and recommended reading**

279 Papers of particular interest, published within the period of review, have been highlighted as:

280 * of special interest

281 ** of outstanding interest

282

283

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