



HAL
open science

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

Marie Tauber, Fang Wang, Brian Kim, Nicolas Gaudenzio

► To cite this version:

Marie Tauber, Fang Wang, Brian Kim, Nicolas Gaudenzio. Bidirectional sensory neuron–immune interactions: a new vision in the understanding of allergic inflammation. *Current Opinion in Immunology*, 2021, 72, pp.79-86. 10.1016/j.coi.2021.03.012 . hal-03663632

HAL Id: hal-03663632

<https://ut3-toulouseinp.hal.science/hal-03663632v1>

Submitted on 24 Apr 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

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

6 Marie Tauber^{1,2*}, Fang Wang^{3,4,5*}, Brian Kim^{3,4,6,7#} and Nicolas Gaudenzio^{1,#}.

7

8 ¹Toulouse Institute for Infectious and Inflammatory Diseases (Infinity), Inserm UMR1291
9 CNRS UMR5051, University of Toulouse III, Toulouse, France

10 ²Department of Dermatology, Toulouse University Hospital, France

11 ³Center for the Study of Itch and Sensory Disorders, Washington University School of
12 Medicine, St. Louis, MO 63110, USA

13 ⁴Division of Dermatology, Department of Medicine, Washington University School of
14 Medicine, St. Louis, MO 63110, USA

15 ⁵Department of Dermatology, The First Affiliated Hospital, Sun Yat-sen University,
16 Guangzhou, Guangdong 510080, China

17 ⁶Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO
18 63110, USA

19 ⁷Department of Pathology and Immunology, Washington University School of Medicine, St.
20 Louis, MO 63110, USA

21

22 *# Equal contributions.

23 Correspondence should be addressed to:

24 briankim@wustl.edu

25 or

26 nicolas.gaudenzio@inserm.fr

27

28

29

30

31

32

33

34

35

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 hyperresponsiveness. 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.

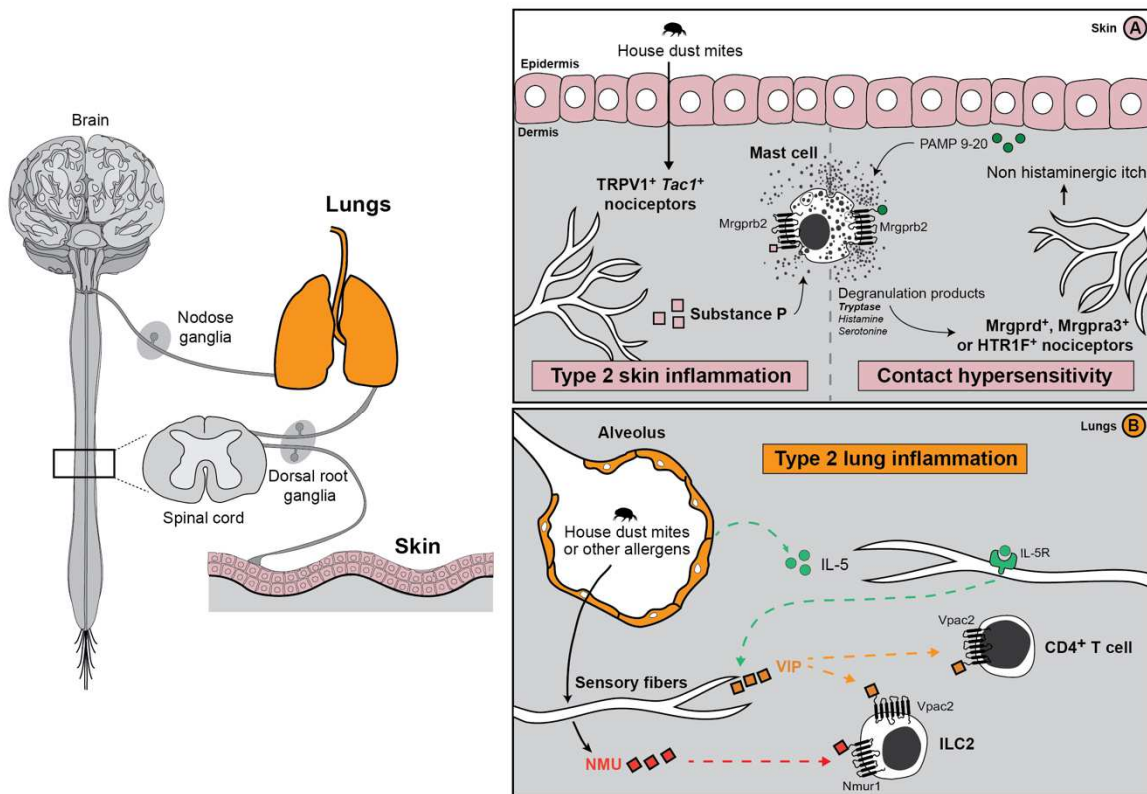
232

233

234

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 trypsinase (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 neuropeptide 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

260 **Acknowledgments**

261 This work was supported by grants from the Société Française de Dermatologie (SFD), the
 262 Société Française d’Allergologie (SFA), the European Research Council (ERC-2018-STG
 263 #802041) and the INSERM ATIP-Avenir program.

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

284 1. Sherrington CS: *Textbook of Physiology*. Pentland; 1900.

285 2. Baliki MN, Apkarian A V: **Nociception, Pain, Negative Moods, and Behavior**
286 **Selection**. *Neuron* 2015, **87**:474–491.

287 3. Tamari M, Ver Heul AM, Kim BS: **Immunosensation: Neuroimmune Cross Talk in**
288 **the Skin**. *Annu Rev Immunol* 2021, **39**.

289 ** This review which has just been published, gives an emerging dynamic picture of the skin
290 as a truly systemic organ with highly coordinated physical, immunologic, and neural
291 functions in barrier immunology.

292 4. Basso L, Serhan N, Tauber M, Gaudenzio N: **Peripheral neurons: Master regulators**
293 **of skin and mucosal immune response**. *Eur J Immunol* 2019, **49**:1984–1997.

294 ** In this review, the authors discuss recent advances in the neural regulation of the immune
295 response, both in physiological and pathological contexts by taking into account the
296 type of organs (lungs, skin and gut), subtypes of peripheral neurons (sympathetic,
297 nociceptive and intrinsic gut neurons) or immune cells and strains of pathogens
298 studied.

299 5. Galli SJ, Gaudenzio N, Tsai M: **Mast Cells in Inflammation and Disease: Recent**
300 **Progress and Ongoing Concerns**. *Annu Rev Immunol* 2020, **38**:49–77.

- 301 ** In this review, the authors describe the origins of tissue mast cells and outline evidence
302 that these cells can have beneficial as well as detrimental functions, both innately and
303 as participants in adaptive immune responses. They also discuss aspects of mast cell
304 heterogeneity and comment on how the plasticity of this lineage may provide insight
305 into its roles in health and disease.
- 306 6. Belmonte C, Viana F: **Molecular and cellular limits to somatosensory specificity.**
307 *Mol Pain* 2008, **4**:14.
- 308 7. Sun YG, Chen ZF: **A gastrin-releasing peptide receptor mediates the itch sensation**
309 **in the spinal cord.** *Nature* 2007, **448**:700–703.
- 310 8. Liu Q, Tang Z, Surdenikova L, Kim S, Patel KN, Kim A, Ru F, Guan Y, Weng HJ,
311 Geng Y, et al.: **Sensory neuron-specific GPCR Mrgprs are itch receptors**
312 **mediating chloroquine-induced pruritus.** *Cell* 2009, **139**:1353–1365.
- 313 9. Franck MC, Stenqvist A, Li L, Hao J, Usoskin D, Xu X, Wiesenfeld-Hallin Z, Ernfors
314 P: **Essential role of Ret for defining non-peptidergic nociceptor phenotypes and**
315 **functions in the adult mouse.** *Eur J Neurosci* 2011, **33**:1385–1400.
- 316 10. Marmigere F, Montelius A, Wegner M, Groner Y, Reichardt LF, Ernfors P: **The**
317 **Runx1/AML1 transcription factor selectively regulates development and survival**
318 **of TrkA nociceptive sensory neurons.** *Nat Neurosci* 2006, **9**:180–187.
- 319 11. Molliver DC, Wright DE, Leitner ML, Parsadanian AS, Doster K, Wen D, Yan Q,
320 Snider WD: **IB4-binding DRG neurons switch from NGF to GDNF dependence in**
321 **early postnatal life.** *Neuron* 1997, **19**:849–861.
- 322 12. Liu Q, Dong X: **The role of the Mrgpr receptor family in itch.** *Handb Exp*
323 *Pharmacol* 2015, **226**:71–88.
- 324 13. Pinto LG, Souza GR, Kusuda R, Lopes AH, Sant’Anna MB, Cunha FQ, Ferreira SH,
325 Cunha TM: **Non-Peptidergic Nociceptive Neurons Are Essential for Mechanical**
326 **Inflammatory Hypersensitivity in Mice.** *Mol Neurobiol* 2019, **56**:5715–5728.
- 327 * Small nerve fibers that bind the isolectin B4 (IB4+ C-fibers) are a subpopulation of primary
328 afferent neurons that are involved in nociceptive sensory transduction and do not
329 express the neuropeptides substance P and calcitonin-gene related peptide (CGRP). In
330 this study, the authors suggest that IB4+ C-fibers are not involved in normal
331 mechanical nociception but are sensitised by inflammatory stimuli and play a crucial
332 role in mediating mechanical inflammatory hypersensitivity.
- 333 14. Snider WD, McMahon SB: **Tackling pain at the source: new ideas about**
334 **nociceptors.** *Neuron* 1998, **20**:629–632.

- 335 15. Usoskin D, Furlan A, Islam S, Abdo H, Lonnerberg P, Lou D, Hjerling-Leffler J,
336 Haeggstrom J, Kharchenko O, Kharchenko P V, et al.: **Unbiased classification of**
337 **sensory neuron types by large-scale single-cell RNA sequencing.** *Nat Neurosci*
338 2015, **18**:145–153.
- 339 16. Zeisel A, Hochgerner H, Lonnerberg P, Johnsson A, Memic F, van der Zwan J, Haring
340 M, Braun E, Borm LE, La Manno G, et al.: **Molecular Architecture of the Mouse**
341 **Nervous System.** *Cell* 2018, **174**:999-+.
- 342 17. Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR,
343 Koltzenburg M, Basbaum AI, Julius D: **Impaired nociception and pain sensation in**
344 **mice lacking the capsaicin receptor.** *Science* 2000, **288**:306–13.
- 345 18. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D: **The**
346 **capsaicin receptor: a heat-activated ion channel in the pain pathway.** *Nature* 1997,
347 **389**:816–824.
- 348 19. Jordt SE, Bautista DM, Chuang HH, McKemy DD, Zygmunt PM, Högestätt ED, Meng
349 ID, Julius D: **Mustard oils and cannabinoids excite sensory nerve fibres through**
350 **the TRP channel ANKTM1.** *Nature* 2004, **427**:260–265.
- 351 20. Chen O, Donnelly CR, Ji RR: **Regulation of pain by neuro-immune interactions**
352 **between macrophages and nociceptor sensory neurons.** *Curr Opin Neurobiol* 2020,
353 **62**:17–25.
- 354 ** In this review, the authors develop the specific role of macrophages in the pathogenesis of
355 pain and describe their bilateral communications with nociceptors, the specialized
356 primary sensory neurons that sense pain. They also discuss a potential pro-resolution
357 role of macrophages in inflammation and pain.
- 358 21. Wang F, Yang TB, Kim BS: **The Return of the Mast Cell: New Roles in**
359 **Neuroimmune Itch Biology.** *J Invest Dermatol* 2020, **140**:945–951.
- 360 ** In this review, the authors exposed that most chronic itch disorders are likely
361 nonhistaminergic in nature. They present an overview of classical mast cell biology
362 and put these concepts into the context of recent advances in our understanding of the
363 regulation and function of the mast cell-nerve unit in itch biology.
- 364 22. Koyuncu Irmak D, Kilinc E, Tore F: **Shared fate of meningeal mast cells and**
365 **sensory neurons in migraine.** *Front Cell Neurosci* 2019, **13**:136.
- 366 * Mast cells and sensory neurons represent both the target and source of the neuropeptides
367 that play autocrine, paracrine, and neuro-endocrine roles during this inflammatory
368 process. This review intends to contribute to a better understanding of the meningeal

- 369 mast cell and sensory neuron bi-directional interactions from molecular, cellular,
370 functional points of view.
- 371 23. Ferreira SH, Lorenzetti BB, Bristow AF, Poole S: **Interleukin-1 beta as a potent**
372 **hyperalgesic agent antagonized by a tripeptide analogue.** *Nature* 1988, **334**:698–
373 700.
- 374 24. Jin X, Gereau RW th: **Acute p38-mediated modulation of tetrodotoxin-resistant**
375 **sodium channels in mouse sensory neurons by tumor necrosis factor-alpha.** *J*
376 *Neurosci* 2006, **26**:246–255.
- 377 25. Richter F, Natura G, Loser S, Schmidt K, Viisanen H, Schaible HG: **Tumor necrosis**
378 **factor causes persistent sensitization of joint nociceptors to mechanical stimuli in**
379 **rats.** *Arthritis Rheum* 2010, **62**:3806–3814.
- 380 26. Bianchi M, Sacerdote P, Ricciardi-Castagnoli P, Mantegazza P, Panerai AE: **Central**
381 **effects of tumor necrosis factor alpha and interleukin-1 alpha on nociceptive**
382 **thresholds and spontaneous locomotor activity.** *Neurosci Lett* 1992, **148**:76–80.
- 383 27. Watkins LR, Wiertelak EP, Goehler LE, Smith KP, Martin D, Maier SF:
384 **Characterization of cytokine-induced hyperalgesia.** *Brain Res* 1994, **654**:15–26.
- 385 28. Ebbinghaus M, Uhlig B, Richter F, von Banchet GS, Gajda M, Brauer R, Schaible HG:
386 **The role of interleukin-1beta in arthritic pain: main involvement in thermal, but**
387 **not mechanical, hyperalgesia in rat antigen-induced arthritis.** *Arthritis Rheum*
388 2012, **64**:3897–3907.
- 389 29. Binshtok AM, Wang H, Zimmermann K, Amaya F, Vardeh D, Shi L, Brenner GJ, Ji
390 RR, Bean BP, Woolf CJ, et al.: **Nociceptors are interleukin-1beta sensors.** *J*
391 *Neurosci* 2008, **28**:14062–14073.
- 392 30. Pinto LG, Cunha TM, Vieira SM, Lemos HP, Verri Jr. WA, Cunha FQ, Ferreira SH:
393 **IL-17 mediates articular hypernociception in antigen-induced arthritis in mice.**
394 *Pain* 2010, **148**:247–256.
- 395 31. Vazquez E, Kahlenbach J, Segond von Banchet G, Konig C, Schaible HG, Ebersberger
396 A: **Spinal interleukin-6 is an amplifier of arthritic pain in the rat.** *Arthritis Rheum*
397 2012, **64**:2233–2242.
- 398 32. Laumet G, Bavencoffe A, Edralin JD, Huo XJ, Walters ET, Dantzer R, Heijnen CJ,
399 Kavelaars A: **Interleukin-10 resolves pain hypersensitivity induced by cisplatin by**
400 **reversing sensory neuron hyperexcitability.** *Pain* 2020, **161**:2344–2352.
- 401 * The authors shows that the anti-inflammatory cytokine IL-10 is able to attenuate pain
402 responses not solely by dampening neuroinflammation. They demonstrate in a model

- 403 of chemotherapy-induced neuropathic pain that endogenous IL-10 prevents transition
404 to chronic pain by binding to IL-10 receptors on sensory neurons to regulate their
405 activity.
- 406 33. Gao X, Han S, Huang Q, He SQ, Ford NC, Zheng Q, Chen Z, Yu S, Dong X, Guan Y:
407 **Calcium imaging in population of dorsal root ganglion neurons unravels novel**
408 **mechanisms of visceral pain sensitization and referred somatic hypersensitivity.**
409 *Pain* 2020, **Publish Ah.**
- 410 * In this study, the authors suggest that 2,4,6-trinitrobenzene sulfonic acid-induced colitis and
411 capsaicin-induced visceral irritation may sensitize L6 dorsal root ganglion (DRG)
412 neurons to colorectal and somatic inputs and also increase the excitability of L4 DRG
413 neurons that do not receive colorectal inputs. It may represent a potential peripheral
414 neuronal mechanism for visceral pain sensitization and referred somatic
415 hypersensitivity.
- 416 34. Sanvictores T, Tadi P: **Neuroanatomy, Autonomic Nervous System Visceral**
417 **Afferent Fibers and Pain.** In *StatPearls.* . 2020.
- 418 35. Wilson SR, The L, Batia LM, Beattie K, Katibah GE, McClain SP, Pellegrino M,
419 Estandian DM, Bautista DM: **The epithelial cell-derived atopic dermatitis cytokine**
420 **TSLP activates neurons to induce itch.** *Cell* 2013, **155**:285–295.
- 421 36. Cevikbas F, Wang X, Akiyama T, Kempkes C, Savinko T, Antal A, Kukova G, Buhl
422 T, Ikoma A, Buddenkotte J, et al.: **A sensory neuron-expressed IL-31 receptor**
423 **mediates T helper cell-dependent itch: Involvement of TRPV1 and TRPA1.** *J*
424 *Allergy Clin Immunol* 2014, **133**:448–460.
- 425 37. Oetjen LK, Mack MR, Feng J, Whelan TM, Niu H, Guo CJ, Chen S, Trier AM, Xu
426 AZ, Tripathi S V., et al.: **Sensory Neurons Co-opt Classical Immune Signaling**
427 **Pathways to Mediate Chronic Itch.** *Cell* 2017, **171**:217-228.e13.
- 428 38. Guttman-Yassky E, Silverberg JI, Nemoto O, Forman SB, Wilke A, Prescilla R, de la
429 Pena A, Nunes FP, Janes J, Gamalo M, et al.: **Baricitinib in adult patients with**
430 **moderate-to-severe atopic dermatitis: A phase 2 parallel, double-blinded,**
431 **randomized placebo-controlled multiple-dose study.** *J Am Acad Dermatol* 2019,
432 **80**:913-921 e9.
- 433 39. Kim BS, Howell MD, Sun K, Papp K, Nasir A, Kuligowski ME, Investigators IS:
434 **Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or**
435 **triamcinolone cream.** *J Allergy Clin Immunol* 2019, doi:10.1016/j.jaci.2019.08.042.
- 436 40. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Kaino H, Nagata T: **Delgocitinib**

- 437 **ointment, a topical Janus kinase inhibitor, in adult patients with moderate to**
438 **severe atopic dermatitis: A phase 3, randomized, double-blind, vehicle-controlled**
439 **study and an open-label, long-term extension study.** *J Am Acad Dermatol* 2020,
440 **82:823–831.**
- 441 41. Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour JP,
442 Spelman L, Katoh N, Saeki H, Poulin Y, et al.: **Tralokinumab for moderate-to-**
443 **severe atopic dermatitis: results from two 52-week, randomized, double-blind,**
444 **multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2).** *Br J*
445 *Dermatol* 2020, doi:10.1111/bjd.19574.
- 446 42. Silverberg JI, Toth D, Bieber T, Alexis AF, Elewski BE, Pink AE, Hijnen D, Jensen
447 TN, Bang B, Olsen CK, et al.: **Tralokinumab plus topical corticosteroids for the**
448 **treatment of moderate-to-severe atopic dermatitis: results from the double-blind,**
449 **randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial.** *Br J*
450 *Dermatol* 2020, doi:10.1111/bjd.19573.
- 451 43. Guttman-Yassky E, Thaci D, Pangan AL, Hong HC, Papp KA, Reich K, Beck LA,
452 Mohamed MF, Othman AA, Anderson JK, et al.: **Upadacitinib in adults with**
453 **moderate to severe atopic dermatitis: 16-week results from a randomized,**
454 **placebo-controlled trial.** *J Allergy Clin Immunol* 2020, **145:877–884.**
- 455 44. Gooderham MJ, Forman SB, Bissonnette R, Beebe JS, Zhang W, Banfield C, Zhu L,
456 Papacharalambous J, Vincent MS, Peeva E: **Efficacy and Safety of Oral Janus**
457 **Kinase 1 Inhibitor Abrocitinib for Patients With Atopic Dermatitis: A Phase 2**
458 **Randomized Clinical Trial.** *JAMA Dermatol* 2019, **155:1371–1379.**
- 459 45. Guttman-Yassky E, Blauvelt A, Eichenfield LF, Paller AS, Armstrong AW, Drew J,
460 Gopalan R, Simpson EL: **Efficacy and Safety of Lebrikizumab, a High-Affinity**
461 **Interleukin 13 Inhibitor, in Adults With Moderate to Severe Atopic Dermatitis: A**
462 **Phase 2b Randomized Clinical Trial.** *JAMA Dermatol* 2020, **156:411–420.**
- 463 46. Simpson EL, Parnes JR, She D, Crouch S, Rees W, Mo M, van der Merwe R:
464 **Tezepelumab, an anti-thymic stromal lymphopoietin monoclonal antibody, in the**
465 **treatment of moderate to severe atopic dermatitis: A randomized phase 2a clinical**
466 **trial.** *J Am Acad Dermatol* 2019, **80:1013–1021.**
- 467 47. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, Silverberg
468 JI, Deleuran M, Kataoka Y, Lacour JP, et al.: **Two Phase 3 Trials of Dupilumab**
469 **versus Placebo in Atopic Dermatitis.** *N Engl J Med* 2016, **375:2335–2348.**
- 470 48. Ruzicka T, Hanifin JM, Furue M, Pulka G, Mlynarczyk I, Wollenberg A, Galus R,

- 471 Etoh T, Mihara R, Yoshida H, et al.: **Anti-Interleukin-31 Receptor A Antibody for**
472 **Atopic Dermatitis.** *N Engl J Med* 2017, **376**:826–835.
- 473 49. Nemoto O, Furue M, Nakagawa H, Shiramoto M, Hanada R, Matsuki S, Imayama S,
474 Kato M, Hasebe I, Taira K, et al.: **The first trial of CIM331, a humanized**
475 **antihuman interleukin-31 receptor A antibody, in healthy volunteers and patients**
476 **with atopic dermatitis to evaluate safety, tolerability and pharmacokinetics of a**
477 **single dose in a randomized, double-blind, placebo-co.** *Br J Dermatol* 2016,
478 **174**:296–304.
- 479 50. Kabashima K, Furue M, Hanifin JM, Pulka G, Wollenberg A, Galus R, Etoh T, Mihara
480 R, Nakano M, Ruzicka T: **Nemolizumab in patients with moderate-to-severe atopic**
481 **dermatitis: Randomized, phase II, long-term extension study.** *J Allergy Clin*
482 *Immunol* 2018, **142**:1121-1130 e7.
- 483 51. Langan SM, Irvine AD, Weidinger S: **Atopic dermatitis.** *Lancet* 2020, **396**:345–360.
- 484 * This review summarises and discuss advances in the understanding of atopic dermatitis and
485 their implications for the prevention and management of the disease, and the need of
486 future researches.
- 487 52. Serhan N, Basso L, Sibilano R, Petitfils C, Meixiong J, Bonnart C, Reber LL, Marichal
488 T, Starkl P, Cenac N, et al.: **House dust mites activate nociceptor–mast cell clusters**
489 **to drive type 2 skin inflammation.** *Nat Immunol* 2019, **20**:1435–1443.
- 490 ** This study demonstrates that widely distributed domestic allergens (house dust mites) can
491 directly activate TRPV1⁺Tac1⁺ nociceptor (producing the neuropeptide substance P)-
492 MrgprB2⁺ Mast cell sensory clusters to drive the development of type 2 skin
493 inflammation and promote an atopic dermatitis-like skin disease in mice.
- 494 53. Meixiong J, Anderson M, Limjunyawong N, Sabbagh MF, Hu E, Mack MR, Oetjen
495 LK, Wang F, Kim BS, Dong X: **Activation of Mast-Cell-Expressed Mas-Related G-**
496 **Protein-Coupled Receptors Drives Non-histaminergic Itch.** *Immunity* 2019,
497 **50**:1163-1171.e5.
- 498 ** This study shows that mast cells activation through the receptor MrgprB2 contributes to
499 non-histaminergic itch. As compared to IgE-FcεRI signaling, MrgprB2-activated mast
500 cells release more tryptase, less histamine and serotonin and excite distinct itch-sensory
501 neuron populations. The authors suggest that mast-cell-associated Mrgprs may be
502 therapeutic targets for itch associated with allergic contact dermatitis.
- 503 54. Wang F, Trier AM, Li F, Kim S, Chen Z, Chai JN, Mack MR, Morrison SA, Hamilton
504 JD, Baek J, et al.: **A basophil-neuronal axis promotes itch.** *Cell* 2021,

505 doi:10.1016/j.cell.2020.12.033.

506 ** Wang et al. show atopic dermatitis-associated inflammation promotes a basophil-
507 leukotriene neuroimmune axis, independent from mast cells, to evoke acute itch flares.
508 Allergen-stimulated basophils release leukotriene C4 and interact with sensory nerves
509 via cysteinyl LT receptor 2 to mediate itch flares.

510 55. Wallrapp A, Riesenfeld SJ, Burkett PR, Abdulnour REE, Nyman J, Dionne D, Hofree
511 M, Cuoco MS, Rodman C, Farouq D, et al.: **The neuropeptide NMU amplifies ILC2-**
512 **driven allergic lung inflammation.** *Nature* 2017, **549**:351–356.

513 56. Said SI, Mutt V: **Potent peripheral and splanchnic vasodilator peptide from**
514 **normal gut.** *Nature* 1970, **225**:863–4.

515 57. Talbot S, Abdulnour REE, Burkett PR, Lee S, Cronin SJF, Pascal MA, Laedermann C,
516 Foster SL, Tran J V., Lai N, et al.: **Silencing Nociceptor Neurons Reduces Allergic**
517 **Airway Inflammation.** *Neuron* 2015, **87**:341–354.

518 58. Talbot S, Doyle B, Huang J, Wang J-C, Ahmadi M, Roberson DP, Yekkirala A, Foster
519 SL, Browne LE, Bean BP, et al.: **Vagal sensory neurons drive mucous cell**
520 **metaplasia.** *J Allergy Clin Immunol* 2020, **0**.

521 * The authors use a nociceptor neuron–blocking strategy (the sodium channel blocker QX-
522 314) to locally silence lung-innervating nociceptors and demonstrate their role in
523 driving pathologic mucous cell metaplasia through substance P secretion in an allergic
524 lung inflammation mouse model. They propose sensory neuron silencing as a potential
525 therapeutic strategy to reverse asthma-mediated mucin imbalance.

526 59. Lilly CM, Bai TR, Shore SA, Hall AE, Drazen JM: **Neuropeptide content of lungs**
527 **from asthmatic and nonasthmatic patients.** *Am J Respir Crit Care Med* 1995,
528 **151**:548–553.

529 60. Barnes PJ: **Neuroeffector mechanisms: the interface between inflammation and**
530 **neuronal responses.** *J Allergy Clin Immunol* 1996, **98**:S73-81; discussion S81-3.

531 61. Myers AC, Kajekar R, Udem BJ: **Allergic inflammation-induced neuropeptide**
532 **production in rapidly adapting afferent nerves in guinea pig airways.** *Am J Physiol*
533 *Lung Cell Mol Physiol* 2002, **282**:L775-81.

534 62. Blake KJ, Baral P, Voisin T, Lubkin A, Pinho-Ribeiro FA, Adams KL, Roberson DP,
535 Ma YC, Otto M, Woolf CJ, et al.: **Staphylococcus aureus produces pain through**
536 **pore-forming toxins and neuronal TRPV1 that is silenced by QX-314.** *Nat*
537 *Commun* 2018, **9**:37.

538 63. Lee S, Jo S, Talbot S, Zhang HXB, Kotoda M, Andrews NA, Puopolo M, Liu PW,

- 539 Jacquemont T, Pascal M, et al.: **Novel charged sodium and calcium channel**
540 **inhibitor active against neurogenic inflammation.** *Elife* 2019, **8**.
- 541 64. Balestrini A, Joseph V, Dourado M, Reese RM, Shields SD, Rougé L, Bravo DD,
542 Chernov-Rogan T, Austin CD, Chen H, et al.: **A TRPA1 inhibitor suppresses**
543 **neurogenic inflammation and airway contraction for asthma treatment.** *J Exp Med*
544 2021, **218**.
- 545 * Transient receptor potential cation channel member A1 (TRPA1) agonists are elevated in
546 human asthmatic airways, and in rodents, TRPA1 is involved in the induction of
547 airway inflammation and hyperreactivity. Here, the discovery and early clinical
548 development of GDC-0334, a highly potent, selective, and orally bioavailable TRPA1
549 antagonist, is described.
- 550 65. Lee J, Yamamoto T, Hayashi S, Kuramoto H, Kadowaki M: **Enhancement of CGRP**
551 **sensory afferent innervation in the gut during the development of food allergy in**
552 **an experimental murine model.** *Biochem Biophys Res Commun* 2013, **430**:895–900.
- 553 66. Bosmans G, Appeltans I, Stakenborg N, Gomez - Pinilla PJ, Florens M V., Aguilera -
554 Lizarraga J, Matteoli G, Boeckxstaens GE: **Vagus nerve stimulation dampens**
555 **intestinal inflammation in a murine model of experimental food allergy.** *Allergy*
556 2019, doi:10.1111/all.13790.
- 557 ** In the field of food allergy, the group of Guy E. Boeckxstaens shows that vagus nerve
558 stimulation can dampen intestinal inflammation in a murine model of food allergy
559 possibly mediated through the dampening of mast cells and the increased phagocytosis
560 of OVA by CX3CR1^{hi} macrophages.
- 561 67. Aguilera-lizarraga J, Florens M V, Viola MF, Jain P, Perna E, Balemans D, Stakenborg
562 N, Theofanous S, Lopez-lopez C, Jaramillo-polanco J, et al.: **Local immune response**
563 **to food antigens drives meal-induced abdominal pain.** *Nature* 2020,
564 doi:10.1038/s41586-020-03118-2.
- 565 ** The authors show that bacterial infection can trigger break of oral tolerance to food
566 antigens leading to food-induced visceral hypersensitivity upon food-antigen re-
567 exposure. OVA-specific IgE antibodies bind to and sensitize tissue-resident mast cells,
568 which are activated upon re-exposure to OVA during feeding and release mediators
569 that sensitize afferent neurons via a H1R-mediated pathway.
- 570 68. Gonzalez-Figueroa P, Roco JA, Papa I, Núñez Villacís L, Stanley M, Linterman MA,
571 Dent A, Canete PF, Vinuesa CG: **Follicular regulatory T cells produce neuritin to**
572 **regulate B cells.** *Cell* 2021, doi:10.1016/j.cell.2021.02.027.

- 573 ** The authors show that follicular regulatory T cells produce an abundance of neuritin
574 protein, which acts directly on B cells to suppress B cell-driven autoimmunity and IgE-
575 mediated allergies by limiting IgE class switch recombination.
- 576 69. Huang S, Ziegler CGK, Austin J, Mannoun N, Vukovic M, Ordovas-Montanes J,
577 Shalek AK, von Andrian UH: **Lymph nodes are innervated by a unique population**
578 **of sensory neurons with immunomodulatory potential.** *Cell* 2020,
579 doi:10.1016/j.cell.2020.11.028.
- 580 ** By combining whole-mount immunolabeling, retrograde neuronal tracing, single-cell
581 genomics, and optogenetic approaches, the authors uncover a bidirectional
582 neuroimmune communication axis in lymph nodes, where sensory neurons not only
583 sense lymph node immune status but also, when activated, modulate gene expression in
584 immune and stromal cells.
- 585 70. Donnelly CR, Jiang C, Andriessen AS, Wang K, Wang Z, Ding H, Zhao J, Luo X, Lee
586 MS, Lei YL, et al.: **STING controls nociception via type I interferon signalling in**
587 **sensory neurons.** *Nature* 2021, doi:10.1038/s41586-020-03151-1.
- 588 ** The authors show that the innate immune regulator STING, a sensor of self- and pathogen-
589 derived DNA, can control nociception via type I interferon signaling and may be a
590 promising new target for treating chronic pain.
- 591 71. Gao X, Zhang D, Xu C, Li H, Caron KM, Frenette PS: **Nociceptive nerves regulate**
592 **haematopoietic stem cell mobilization.** *Nature* 2020, doi:10.1038/s41586-020-03057-
593 y.
- 594 ** The authors show that nociceptors are required for enforced haematopoietic stem cells
595 (HSCs) mobilization in the bone marrow via the secretion of calcitonin gene-related
596 peptide (CGRP). CGRP but not substance P acts directly on HSCs via RAMP1
597 (receptor activity modifying protein 1) and CALCRL (calcitonin receptor-like receptor)
598 to promote egress by activating a cAMP-mediated signaling pathway.
- 599 72. Worm M, Simpson EL, Thaci D, Bissonnette R, Lacour JP, Beissert S, Kawashima M,
600 Ferrandiz C, Smith CH, Beck LA, et al.: **Efficacy and Safety of Multiple Dupilumab**
601 **Dose Regimens After Initial Successful Treatment in Patients With Atopic**
602 **Dermatitis: A Randomized Clinical Trial.** *JAMA Dermatol* 2020, **156**:131–143.
- 603 73. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, Beck
604 LA, Guttman-Yassky E, Pariser D, Blauvelt A, et al.: **Efficacy and Safety of**
605 **Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic**
606 **Dermatitis: A Phase 3 Randomized Clinical Trial.** *JAMA Dermatol* 2020, **156**:44–

- 607 56.
- 608 74. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D,
609 Simpson EL, Papp KA, Hong HC, Rubel D, et al.: **Long-term management of**
610 **moderate-to-severe atopic dermatitis with dupilumab and concomitant topical**
611 **corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-**
612 **blinded, placebo-controlled, phase 3 trial.** *Lancet* 2017, **389**:2287–2303.
- 613
- 614
- 615