Interactions of the Neuro–Immune–Stromal Triad in Itch

Pang-Yen Tseng[1] and Mark A. Hoon[1]

This review focuses on recent advances in understanding the mechanisms involved in itch signaling in the skin and how these new findings fit into the wider picture of the expression of itch mediators and their receptors in the dermal layer. Because at present studies mostly concentrate on single cellular compartments (e.g., neural alone), we suggest that they may miss important interactions with other compartments. Therefore, to fully appreciate pruritus, we propose that studies should consider (e.g., using transcriptomic information) signal transmission within the entire neuro–immune–stromal triad.

Journal of Investigative Dermatology (2022) **142,** 42–46; doi:10.1016/j.jid.2021.08.443

ITCH-SPECIFIC SENSORY NEURONS

For many years, itch sensation was considered to be a mild form of pain in a model where itch was posited to trigger a low-intensity activation of nociceptive sensory neurons, whereas pain was suggested to evoke strong activation, and central circuits interpret these intensity differences generating separate sensations (Melzack and Wall, 1965; Ross, 2011). However, with the identification and characterization of an itch-specific neurotransmitter, GRP and its receptor, GRPR (Sun and Chen, 2007; Sun et al., 2009), another model become favored. This model postulated that there are separate or partially discrete receptor sensory neurons that activate separate pain and itch neural pathways. Functional studies in mice uncovered at least two cell populations tuned to detect pruritogens by virtue of the genes they express (Han et al., 2013; Mishra and Hoon, 2013; Solinski et al., 2019b; Xing et al., 2020). One neural subtype selectively expresses natriuretic polypeptide B (NPPB), an itch-specific neuropeptide; the second subtype expresses selectively the itch receptor MRGPRA3 (Han et al., 2013; Liu et al., 2009). Several single-cell RNA sequencing (scRNA-seq) studies confirmed these populations (Li et al., 2016; Nguyen et al., 2017; Sharma et al., 2020; Usoskin et al., 2015; Zeisel et al., 2018) (Figure 1a). Importantly, when these cell classes are activated, scratching is triggered (Huang et al., 2018; Sun et al., 2017).

DERMAL IMMUNE AND STROMAL CELLS

Although sensory neurons are key to itch sensation, it is well-known that immune cells are also involved because they release pruritogens. To understand the underlying causation of chronic itch, it is critical to consider changes in cell profiles that occur during inflammation and reflect on which of these are relevant for pruritus. For this reason, we analyzed scRNA-seq data of dermal immune and stromal cells from human atopic dermatitis (AD) samples (Reynolds et al., 2021) (Figure 1b and c). On disruption of the dermal barrier, innate and adaptive immunity is stimulated, and these result in physical, chemical, and cellular responses that protect against potential pathogens (Veiga-Fernandes and Mucida, 2016). Stromal cells affect repair after injury, and this remodeling of the skin may also lead to pruritus (Xu et al., 2020). Therefore, itch can be a consequence of collateral damage caused by a defense against pathogens, by tissue repair, as well as by direct stimulation of sensory neurons by pruritogens.

ITCH MEDIATORS AND THEIR INTERCELLULAR ACTIVATION OF RECEPTORS

In this section, we examine the examples of mediator receptor interactions where transcriptomic data help to define potential under-acknowledged connections. Because of space restraints, we are unable to comprehensively mention all the interactions (Wang and Kim, 2020). Instead, we highlight instances that we hope provoke a view of pruritus from the vantage point of an interconnected network of dermal cell types being involved in the generation of itch. Because data for human sensory neurons are unavailable, our analysis is limited to data from mouse dorsal root ganglia. In addition, because single-cell sequencing may not reveal low expression transcripts and because we only analyzed human AD skin cells, some interactions may be missed (Nguyen et al., 2017). We would also like to recognize that transcriptional expression does not guarantee functional significance (e.g., pruriceptor genes not only need to be transcribed but must also be translated, processed, and appropriately localized (Zheng et al., 2014).

MAST CELLS

Release of agents from mast cells elicits pruritus by direct activation of itch neurons, and they express all the biosynthetic apparatus to achieve this (Figure 1e) (Buhl et al., 2020; Reddy et al., 2015; Solinski et al., 2019b; Voisin et al., 2021). These agents include histamine, serotonin, leukotrienes, and sphingosine-1-phosphate (Stone et al., 2010) (Figure 1e). NPPB and MRGPRA3 neurons predominantly express

[1]*Molecular Genetics Section, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, Maryland, USA*

Correspondence: Mark A. Hoon, Molecular Genetics Section, National Institutes of Dental and Craniofacial Research, National Institute of Health, 35 Convent Drive, Bethesda, Maryland 20892, USA. E-mail: mark.hoon@nih.gov

Abbreviations: AD, atopic dermatitis; DC, dendritic cell; KC, keratinocyte; NPPB, natriuretic polypeptide B; scRNA-seq, single-cell RNA sequencing; Th2, T helper type 2

Received 1 July 2021; revised 2 August 2021; accepted 9 August 2021; accepted manuscript published online 16 October 2021; corrected proof published online 18 November 2021

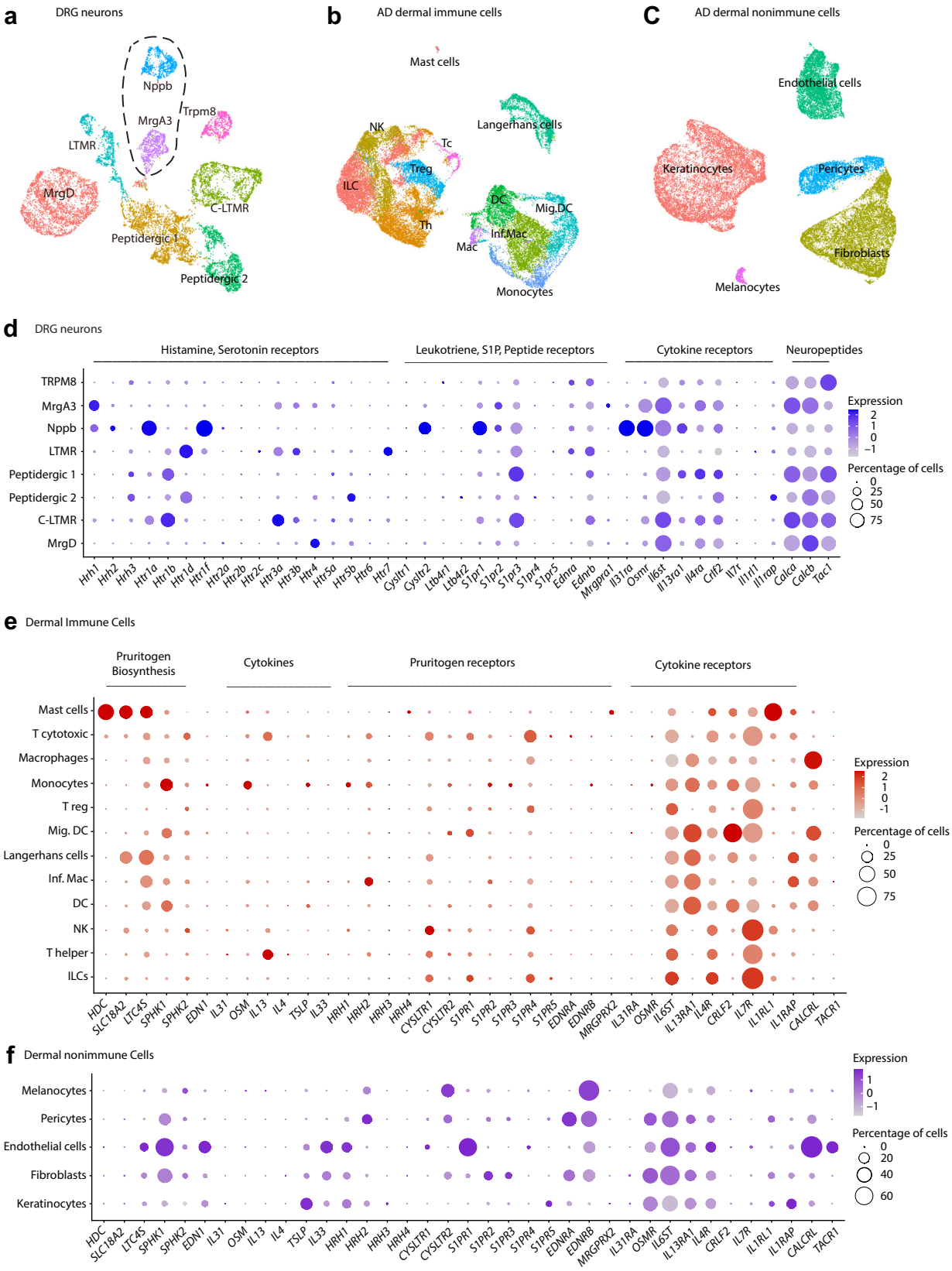

Figure 1. Analysis of scRNA-seq for the neuro–immune–stromal triad. UMAP analyses of scRNA-seq of (**a**) 11,139 mouse DRG neurons (GSE139088) (Sharma et al., 2020), (**b**) 31,087 dermal immune cells from patients with AD, and (**c**) 63,512 dermal stromal cells from patients with AD (https://developmentcellatlas.ncl.ac.uk/datasets/hca_skin_portal/) (Reynolds et al., 2021). This approach reduces transcriptomic information from each sequenced cell to a single point, with distances between points reflecting the heterogeneity of the data between cells and cells with similar expression profiles clustering; for example, itch neurons (circled) form individual clusters that are segregated from other neurons. Clusters are named on the basis of prominent genes that define functions or accepted classifications: MRGD (polymodal nociceptor), LTMR, C-fiber LTMRs, TRPM8 (cold receptors), peptidergic (expressing CGRP and substance P), NPPB and

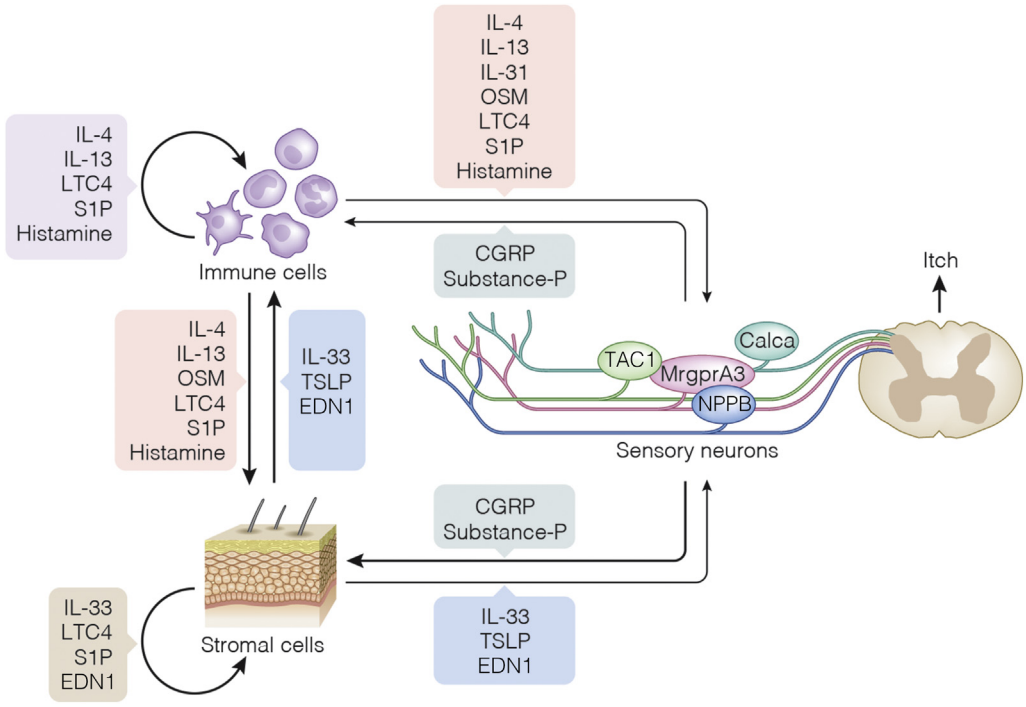

Figure 2. Interactions between neurons, immune cells, and stromal cells related to pruritus. Summary schematic of the major itch mediator and receptor interactions in the neuro–immune–stromal triad. NPPB, natriuretic polypeptide B. *Scientific illustration services provided by KatieRisVicari.com.*

histamine receptor HRH1, and HRH2 is expressed exclusively by NPPB neurons (Figure 1d). Receptors for serotonin (HTR1A and HTR1F) and lipid mediators leukotriene (CYSLTR2) and sphingosine-1-phosphate (S1PR1) are also found in NPPB neurons (Figure 1d) (Solinski et al., 2019b; Voisin et al., 2021), but the physiological relevance of serotonin receptors is unclear. In addition to stimulating neurons, histamine activates other stromal cells, especially endothelial cells, to increase vascular permeability (Ashina et al., 2015). This fits well with the psychophysical observation that intradermal injection of histamine causes pricking, stinging, and burning sensations as well as skin flare and wheal (Sikand et al., 2009). Together with other agents released from mast cells, which also activate multiple cell targets, this shows the complexity of interactions that occur when mast cells release granules (Figures 1d–f and 2). Furthermore, additional cell classes, including basophils, release these same mediators to induce itch (Wang et al., 2021).

LYMPHOID CELLS

Cytokines are another major class of secreted transmitters whose expression is elevated in inflammatory skin disease (Wang and Kim, 2020). Historically, cytokines were thought to be released from immune and stromal cells regulating the recruitment, maturation, growth, and responsiveness of these populations. Perhaps because of this focus, their effect on neurons was overlooked for many years. scRNA-seq data reveal that sensory neurons express a restricted set of abundantly expressed cytokine receptors (Figure 1d). These patterns of expression agree with findings showing that IL-4 and IL-13 potentiate itch responses in mice (Campion et al., 2019; Oetjen et al., 2017). The source of IL-31 and IL-13 is predominantly T cells (Cevikbas et al., 2014; Dillon et al., 2004; Veiga-Fernandes and Mucida, 2016), and IL-4 is initially released from mast cells, eosinophils, and basophils, but then, by positive feedback, it is released by T helper type 2 (Th2) cells (Gieseck et al., 2018). In addition, certain classes of innate lymphoid cells are elevated in inflamed skin diseases, and the cytokines they produce may have effects on pruritus (Bielecki et al., 2021; Kim et al., 2013; van der Ploeg et al., 2021). Overexpression of IL-13 is most prominent in AD (Tsoi et al., 2019), with other inflammatory skin diseases showing elevated expression of different combinations of cytokines (Nograles et al., 2010). Notably, during injection, cytokines elicit direct albeit delayed mild scratch responses in mice, implicating them as potentiators of itch (Campion et al., 2019). Murine and human itch neurons express IL-31RA, and mouse itch neurons express IL-4RA and IL-13RA (Chiu et al., 2014; Oetjen et al., 2017; Solinski et al., 2019a). With the exception of IL-31RA, which is selectively

MRGA3 (pruriceptors), Th, Tc, Treg, NK, ILCs, Mig.DC, DCs, Inf.Mac, and Macs. (**d–f**) Indicated genes (https://www.uniprot.org/) are shown for (**d**) DRG, (**e**) immune cells, and (**f**) stromal cells. Color bars indicate scaled average gene expression levels within the clusters. Dot sizes indicate the fractions of cells in a population that express given genes. AD, atopic dermatitis; DC, dendritic cell; DRG, dorsal root ganglion; ILC, innate lymphoid cell; Inf.Mac, inflammatory macrophage; LTMR, low-threshold mechanoreceptor; Mac, macrophage; Mig.DC, migratory dendritic cell; NPPB, natriuretic polypeptide B; scRNA-seq, single-cell RNA sequencing; ILCs, innate lymphoid cells; Tc, cytotoxic T cells; Th, T helper cells; Treg, regulatory T cell; UMAP, Uniform Manifold Approximation and Projection.

expressed in a specific population of NPPB neurons but in no other neurons (Figure 1d and f), receptors for these cytokines are expressed broadly in several classes of immune cells, consistent with their role in promoting Th2 inflammation. In addition, stromal cells express IL-4RA and IL-13RA, pointing to IL-4 and IL-13 acting in all dermal cellular compartments. Furthermore, because IL-4RA and IL-13RA are expressed in many classes of nociceptors, these cytokines are likely also involved in pain (Usoskin et al., 2015).

STROMAL CELLS

Stromal cells of the skin, such as keratinocytes (KCs), endothelial cells, pericytes, and fibroblasts, are not passive bystanders during inflammation producing bioactive peptides involved in itch and expressing receptors to several classes of mediators (Figure 1f). Several substances produced by stromal cells are reported to elicit itch reactions, including IL-33, TSLP, and endothelin (Imai, 2019). Although Il-33 and endothelin are prominently released by endothelial cells, they are also reported to be secreted by immune cells (Imai, 2019) and are expressed by KCs. IL-33 belongs to the IL-1 superfamily of cytokines and potently induces Th2 inflammation. Its receptor, IL-1RL1, together with IL-1RAP are coupled to the production of type 2 cytokines in polarized Th2 cells. Therefore, a major effect of IL-33 occurs through the activation of immune cells and the consequent release of pruritogens. In addition, IL-33 likely acts on KCs (Figure 1f). Similar to IL-33, TSLP, expressed by KCs, activates immune cells, and there is an abundant expression of its heteromeric receptors, CRLF2 and IL7R, in this cell compartment. Notably, TSLP activates mast cells, monocytes, dendritic cells (DCs), and Langerhans cells; therefore it has pleiotropic effects on the immune system and is part of the long-term changes in inflamed skin (Han et al., 2017; Liu et al., 2019). In addition, IL-33 and TSLP have been shown to directly stimulate sensory neurons (Liu et al., 2016; Wilson et al., 2013). In contrast to IL-33 and TSLP, endothelin acts mainly on pericytes and fibroblasts through its receptors, EDNRA and EDNRB, which leads to vasoconstriction and tissue remodeling. In addition, both receptors are broadly expressed by several subtypes of sensory neurons, which are critical for endothelin-induced itch and nociception (Magnúsdóttir et al., 2020).

SENSORY NEURONS

It has become apparent that sensory neurons not only detect pruritogens but can signal to dermal cells. The major peptides released are CGRPs (CALCA and CALCB) and substance P (TAC1), which are expressed in a broad population of neurons encompassing many types of nociceptors (Figure 1f). Congruous with CGRP and substance P being potent vasodilators, their receptors, CALCRL and TACR1, are found in stromal cells, and neurogenic inflammation associated with injury is thought to be the result of these interactions (Basbaum et al., 2009). Of note, for pruritus, CGRP can activate multiple classes of immune cells (Figure 1e), activating DC (Kashem et al., 2015), promoting psoriasis (Ostrowski et al., 2011), and altering the balance of infiltrating immune cells (Baral et al., 2018; Nagashima et al., 2019; Pinho-Ribeiro et al., 2018). Similar to CGRP, substance P activates multiple classes of immune cells through its canonical receptor, TACR1 (Payan et al., 1983). However, in addition to TACR1, substance P activates MRGPRX2 found on mast cells (Azimi et al., 2017; McNeil et al., 2015) and MRGPRA1 in sensory neurons (Azimi et al., 2016), and substance P can stimulate MRGPRA1 in DCs initiating Th2 responses (Perner et al., 2020).

SUMMARY

Skin is a barrier to the external environment, and when it is damaged, a variety of protective strategies are employed. First, skin harbors the detectors for a plethora of challenges, including the well-recognized responses of the immune system and sensory neurons (Figure 2). Second, it has an array of defense strategies to repel invaders with immune and stromal cells delivering innate and acquired immunity and the sensory nerve system evoking scratching and other behavioral reactions. We propose that researchers in the itch field should consider this interplay when trying to decipher the mechanisms underlying pruritus.

ORCIDs

Pang-Yen Tseng: http://orcid.org/0000-0003-2039-0002
Mark A. Hoon: http://orcid.org/0000-0002-8794-1684

CONFLICT OF INTEREST

MAH is a patent holder on a National Institutes of Health patent for the use of natriuretic polypeptide B antagonists in the treatment of pruritus. The remaining author states no conflict of interest.

ACKNOWLEDGMENTS

This work was supported by the intramural research program of the National Institute of Dental and Craniofacial Research, National Institutes of Health (project ZIADE000721-21 to MAH).

AUTHOR CONTRIBUTIONS

Conceptualization: PYT, MAH; Writing: PYT, MAH; Writing – Original Draft Preparation: PYT, MAH; Writing – Review and Editing: MAH

REFERENCES

Ashina K, Tsubosaka Y, Nakamura T, Omori K, Kobayashi K, Hori M, et al. Histamine induces vascular hyperpermeability by increasing blood flow and endothelial barrier disruption in vivo. PLoS One 2015;10:e0132367.

Azimi E, Reddy VB, Pereira PJS, Talbot S, Woolf CJ, Lerner EA. Substance P activates Mas-related G protein-coupled receptors to induce itch. J Allergy Clin Immunol 2017;140:447–53.e3.

Azimi E, Reddy VB, Shade KC, Anthony RM, Talbot S, Pereira PJS, et al. Dual action of neurokinin-1 antagonists on Mas-related GPCRs. JCI Insight 2016;1:e89362.

Baral P, Umans BD, Li L, Wallrapp A, Bist M, Kirschbaum T, et al. Nociceptor sensory neurons suppress neutrophil and γδ T cell responses in bacterial lung infections and lethal pneumonia [published correction appears in Nat Med 2018;24:1625–6]. Nat Med 2018;24:417–26.

Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell 2009;139:267–84.

Bielecki P, Riesenfeld SJ, Hütter JC, Torlai Triglia E, Kowalczyk MS, Ricardo-Gonzalez RR, et al. Skin-resident innate lymphoid cells converge on a pathogenic effector state. Nature 2021;592:128–32.

Buhl T, Ikoma A, Kempkes C, Cevikbas F, Sulk M, Buddenkotte J, et al. Protease-activated receptor-2 regulates neuro-epidermal communication in atopic dermatitis. Front Immunol 2020;11:1740.

Campion M, Smith L, Gatault S, Métais C, Buddenkotte J, Steinhoff M. Interleukin-4 and interleukin-13 evoke scratching behaviour in mice. Exp Dermatol 2019;28:1501–4.

Cevikbas F, Wang X, Akiyama T, Kempkes C, Savinko T, Antal A, et al. A sensory neuron-expressed IL-31 receptor mediates T helper cell-dependent itch: involvement of TRPV1 and TRPA1. J Allergy Clin Immunol 2014;133:448–60.

Chiu IM, Barrett LB, Williams EK, Strochlic DE, Lee S, Weyer AD, et al. Transcriptional profiling at whole population and single cell levels reveals somatosensory neuron molecular diversity [published correction appears in Elife 2015;4:e06720]. Elife 2014;3:e04660.

Dillon SR, Sprecher C, Hammond A, Bilsborough J, Rosenfeld-Franklin M, Presnell SR, et al. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice [published correction appears in Nat Immunol 2005;6:114]. Nat Immunol 2004;5:752–60.

Gieseck RL 3rd, Wilson MS, Wynn TA. Type 2 immunity in tissue repair and fibrosis. Nat Rev Immunol 2018;18:62–76.

Han H, Roan F, Ziegler SF. The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines. Immunol Rev 2017;278:116–30.

Han L, Ma C, Liu Q, Weng HJ, Cui Y, Tang Z, et al. A subpopulation of nociceptors specifically linked to itch. Nat Neurosci 2013;16:174–82.

Huang J, Polgár E, Solinski HJ, Mishra SK, Tseng PY, Iwagaki N, et al. Circuit dissection of the role of somatostatin in itch and pain [published correction appears in Nat Neurosci 2018;21:894]. Nat Neurosci 2018;21:707–16.

Imai Y. Interleukin-33 in atopic dermatitis. J Dermatol Sci 2019;96:2–7.

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 [published correction appears in Immunity 2015;43:830]. Immunity 2015;43:515–26.

Kim BS, Siracusa MC, Saenz SA, Noti M, Monticelli LA, Sonnenberg GF, et al. TSLP elicits IL-33-independent innate lymphoid cell responses to promote skin inflammation. Sci Transl Med 2013;5:170ra16.

Li CL, Li KC, Wu D, Chen Y, Luo H, Zhao JR, et al. Somatosensory neuron types identified by high-coverage single-cell RNA-sequencing and functional heterogeneity. Cell Res 2016;26:967.

Liu B, Tai Y, Achanta S, Kaelberer MM, Caceres AI, Shao X, et al. IL-33/ST2 signaling excites sensory neurons and mediates itch response in a mouse model of poison ivy contact allergy. Proc Natl Acad Sci USA 2016;113:E7572–9.

Liu B, Tai Y, Liu B, Caceres AI, Yin C, Jordt SE. Transcriptome profiling reveals Th2 bias and identifies endogenous itch mediators in poison ivy contact dermatitis. JCI Insight 2019;5:e124497.

Liu Q, Tang Z, Surdenikova L, Kim S, Patel KN, Kim A, et al. Sensory neuron-specific GPCR Mrgprs are itch receptors mediating chloroquine-induced pruritus. Cell 2009;139:1353–65.

Magnúsdóttir EI, Grujic M, Bergman J, Pejler G, Lagerström MC. Mouse connective tissue mast cell proteases tryptase and carboxypeptidase A3 play protective roles in itch induced by endothelin-1. J Neuroinflammation 2020;17:123.

McNeil BD, Pundir P, Meeker S, Han L, Undem BJ, Kulka M, et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. Nature 2015;519:237–41.

Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965;150:971–9.

Mishra SK, Hoon MA. The cells and circuitry for itch responses in mice. Science 2013;340:968–71.

Nagashima H, Mahlakõiv T, Shih HY, Davis FP, Meylan F, Huang Y, et al. Neuropeptide CGRP limits group 2 innate lymphoid cell responses and constrains type 2 inflammation. Immunity 2019;51:682–95.e6.

Nguyen MQ, Wu Y, Bonilla LS, von Buchholtz LJ, Ryba NJP. Diversity amongst trigeminal neurons revealed by high throughput single cell sequencing. PLoS One 2017;12:e0185543.

Nograles KE, Davidovici B, Krueger JG. New insights in the immunologic basis of psoriasis. Semin Cutan Med Surg 2010;29:3–9.

Oetjen LK, Mack MR, Feng J, Whelan TM, Niu H, Guo CJ, et al. Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. Cell 2017;171:217–28.e13.

Ostrowski SM, Belkadi A, Loyd CM, Diaconu D, Ward NL. Cutaneous denervation of psoriasiform mouse skin improves acanthosis and inflammation in a sensory neuropeptide-dependent manner. J Invest Dermatol 2011;131:1530–8.

Payan DG, Brewster DR, Goetzl EJ. Specific stimulation of human T lymphocytes by substance P. J Immunol 1983;131:1613–5.

Perner C, Flayer CH, Zhu X, Aderhold PA, Dewan ZNA, Voisin T, et al. Substance P release by sensory neurons triggers dendritic cell migration and initiates the type-2 immune response to allergens. Immunity 2020;53:1063–77.e7.

Pinho-Ribeiro FA, Baddal B, Haarsma R, O'Seaghdha M, Yang NJ, Blake KJ, et al. Blocking neuronal signaling to immune cells treats streptococcal invasive infection. Cell 2018;173:1083–97.e22.

Reddy VB, Sun S, Azimi E, Elmariah SB, Dong X, Lerner EA. Redefining the concept of protease-activated receptors: cathepsin S evokes itch via activation of Mrgprs. Nat Commun 2015;6:7864.

Reynolds G, Vegh P, Fletcher J, Poyner EFM, Stephenson E, Goh I, et al. Developmental cell programs are co-opted in inflammatory skin disease. Science 2021;371:eaba6500.

Ross SE. Pain and itch: insights into the neural circuits of aversive somatosensation in health and disease. Curr Opin Neurobiol 2011;21:880–7.

Sharma N, Flaherty K, Lezgiyeva K, Wagner DE, Klein AM, Ginty DD. The emergence of transcriptional identity in somatosensory neurons. Nature 2020;577:392–8.

Sikand P, Shimada SG, Green BG, LaMotte RH. Similar itch and nociceptive sensations evoked by punctate cutaneous application of capsaicin, histamine and cowhage. Pain 2009;144:66–75.

Solinski HJ, Dranchak P, Oliphant E, Gu X, Earnest TW, Braisted J, et al. Inhibition of natriuretic peptide receptor 1 reduces itch in mice. Sci Transl Med 2019a;11:eaav5464.

Solinski HJ, Kriegbaum MC, Tseng PY, Earnest TW, Gu X, Barik A, et al. Nppb neurons are sensors of mast cell-induced itch. Cell Rep 2019b;26:3561–73.e4.

Stone KD, Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. J Allergy Clin Immunol 2010;125(Suppl. 2):S73–80.

Sun S, Xu Q, Guo C, Guan Y, Liu Q, Dong X. Leaky gate model: intensity-dependent coding of pain and itch in the spinal cord. Neuron 2017;93:840–53.e5.

Sun YG, Chen ZF. A gastrin-releasing peptide receptor mediates the itch sensation in the spinal cord. Nature 2007;448:700–3.

Sun YG, Zhao ZQ, Meng XL, Yin J, Liu XY, Chen ZF. Cellular basis of itch sensation. Science 2009;325:1531–4.

Tsoi LC, Rodriguez E, Degenhardt F, Baurecht H, Wehkamp U, Volks N, et al. Atopic dermatitis is an IL-13-dominant disease with greater molecular heterogeneity compared to psoriasis. J Invest Dermatol 2019;139:1480–9.

Usoskin D, Furlan A, Islam S, Abdo H, Lönnerberg P, Lou D, et al. Unbiased classification of sensory neuron types by large-scale single-cell RNA sequencing. Nat Neurosci 2015;18:145–53.

van der Ploeg EK, Hermans MAW, van der Velden VHJ, Dik WA, van Daele PLA, Stadhouders R. Increased group 2 innate lymphoid cells in peripheral blood of adults with mastocytosis. J Allergy Clin Immunol 2021;147:1490–6.e2.

Veiga-Fernandes H, Mucida D. Neuro-immune interactions at barrier surfaces. Cell 2016;165:801–11.

Voisin T, Perner C, Messou MA, Shiers S, Ualiyeva S, Kanaoka Y, et al. The $CysLT_2R$ receptor mediates leukotriene C_4-driven acute and chronic itch. Proc Natl Acad Sci USA 2021;118:e2022087118.

Wang F, Kim BS. Itch: a paradigm of neuroimmune crosstalk. Immunity 2020;52:753–66.

Wang F, Trier AM, Li F, Kim S, Chen Z, Chai JN, et al. A basophil-neuronal axis promotes itch. Cell 2021;184:422–40.e17.

Wilson SR, Thé L, Batia LM, Beattie K, Katibah GE, McClain SP, et al. The epithelial cell-derived atopic dermatitis cytokine TSLP activates neurons to induce itch. Cell 2013;155:285–95.

Xing Y, Chen J, Hilley H, Steele H, Yang J, Han L. Molecular signature of pruriceptive $MrgprA3^+$ neurons. J Invest Dermatol 2020;140:2041–50.

Xu J, Zanvit P, Hu L, Tseng PY, Liu N, Wang F, et al. The cytokine TGF-β induces interleukin-31 expression from dermal dendritic cells to activate sensory neurons and stimulate wound itching. Immunity 2020;53:371–83.e5.

Zeisel A, Hochgerner H, Lönnerberg P, Johnsson A, Memic F, van der Zwan J, et al. Molecular architecture of the mouse nervous system. Cell 2018;174:999–1014.e22.

Zheng CL, Kawane S, Bottomly D, Wilmot B. Analysis considerations for utilizing RNA-Seq to characterize the brain transcriptome. Int Rev Neurobiol 2014;116:21–54.