

Tasting type 2 inflammation in the airways

Robert J. Snelgrove, PhD, and Clare M. Lloyd, PhD London, United Kingdom

Key words: Type 2 immunity, type 2 innate lymphoid cells, tuft cells, epithelial cells, thymic stromal lymphopoietin, IL-25, chronic rhinosinusitis with nasal polyps, solitary chemosensory cell

Central to the induction of type 2 immunity is a complex microenvironmental cross-talk between tissue-resident and inflammatory cells, which sense disparate extrinsic stimuli, such as allergens or helminths, and coordinate a tightly regulated tissue-specific response. In recent years, type 2 innate lymphoid cells (ILC2s) have emerged as highly responsive early effectors in patients with type 2 inflammation, whereby they can function as a prominent source of the traditional T_H2 cytokines IL-5, IL-9, and IL-13 long before an adaptive response is initiated. ILC2 activation is independent of classical antigen-specific activation but is instead driven by cytokines and stress signals released from localized tissue-resident cells after disruption of tissue homeostasis. Conventional signals capable of driving ILC2 growth and cytokine production include the prototypically epithelium-derived cytokines IL-33, thymic stromal lymphopoietin, and IL-25. Although the importance of these cytokines in induction of type 2 inflammation is now largely irrefutable, their exact cellular source and mechanisms defining their release remain more ambiguous.

A series of seminal articles have demonstrated previously that a rare population of specialized taste-chemosensory epithelial cells called tuft cells are the exclusive source of IL-25 within the mouse intestine.¹⁻³ This population was readily expanded upon parasite infection, whereby ILC2-derived IL-13 acted on epithelial crypt progenitors to shift their differentiation toward the tuft cell lineage, thus highlighting a feed-forward positive reaffirming circuit between tuft cells and ILC2s to promote type 2 immunity. Tuft cell ablation² or loss of their chemosensory capacity³ resulted in a defective type 2 response, ablated goblet cell hyperplasia, and compromised helminth expulsion. Furthermore, it was suggested that tuft cells within the tracheas of mice were also the primary source of IL-25.¹ However, the specific cellular source of IL-25 in the upper respiratory tract of human subjects had not been determined.

In the study by Kohanski et al⁴ published in this issue of the *Journal of Allergy and Clinical Immunology*, the authors

demonstrate that solitary chemosensory cells (SCCs) expressing the taste-associated G protein gustducin and the tuft cell marker doublecortin-like kinase 1 (DCAMKL1) are likely the predominant source of IL-25 in the human upper airways. Furthermore, this population was expanded within the nasal polyp tissue of patients with chronic rhinosinusitis with nasal polyps (CRSwNP), which was potentially rationalized by the observed capacity of IL-13 to drive SCC proliferation and IL-25 secretion *in vitro*.

SCCs are specialized chemoresponsive sentinel cells present in the nasal and respiratory epithelium, which respond to diverse noxious stimuli to activate polymodal nociceptors of the trigeminal nerve. Activation of the trigeminal nerve evokes protective reflexes, including sneezing, coughing, apnea, and local neurogenic inflammation of the mucosa.⁵ Although free intraepithelial nerve endings can detect certain irritants, SCCs are anticipated to function as an intermediary to specific irritants to enhance the chemoresponsive capabilities of the trigeminal system. SCCs express many components of the bitter taste signaling pathway, and ligation of their Tas2R bitter taste receptors evokes a signal transduction cascade that culminates in excitation of the trigeminal pain fibers that innervate these chemosensory cells. Although the IL-25-expressing cells described by Kohanski et al⁴ express the taste-associated G protein gustducin, future studies should look to further characterize this population both phenotypically and functionally. Are the SCC-like cells producing IL-25 in the upper airways associated with trigeminal nerves, and do isolated populations of these cells respond to classical bitter taste receptor ligands? Although the authors demonstrate that IL-13 is a potent inducer of SCC expansion and IL-25 release, it will be interesting to define whether the classical capacity of these cells to respond to bitter taste receptor agonists potentiates IL-25 production.

CRSwNP is a prevalent and heterogeneous disease of the sinonasal tracts and nasal cavities associated with T_H2 -dominant inflammation, which affects 5% to 10% of the population. Previous studies have demonstrated increased expression of IL-25 and its receptor (IL-17RB) in the mucosa of patients with CRSwNP, and a neutralizing antibody to IL-25 reduced the number of nasal polyps in a murine model.⁶ The striking expansion of IL-25⁺ SCCs in the polyp tissue of patients with CRSwNP reported by Kohanski et al⁴ and the capacity of IL-13 to drive this expansion *in vitro* is suggestive that a similar SCC (through IL-25)–ILC2 (through IL-13) crosstalk can operate in the upper airways, as seen with tuft cells and ILC2s in the gut.¹⁻³ Accordingly, IL-13 levels and ILC2 numbers are increased in patients with CRSwNP, associated with T_H2 cells and eosinophils, and implicated in polyp formation.^{7,8} The capacity of SCC-derived IL-25 to activate resident ILC2s and potentiate IL-13 release would ultimately augment mucus release, which would be conducive with other SCC-mediated effector reflexes designed to expel and flush out noxious irritants (Fig 1). Moreover, the capacity of SCCs to modulate ILC2 activity aligns more broadly with recent studies defining the capacity of tissue sensory neurons to release neuropeptides in response to a

From Inflammation Repair and Development, National Heart and Lung Institute, Imperial College London.

R.J.S. (209458/Z/17/Z) and C.M.L. (086718/Z/08/Z) are Wellcome Trust–funded Senior Research Fellows in Basic Biomedical Sciences.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication May 16, 2018; accepted for publication June 11, 2018.

Corresponding author: Robert J. Snelgrove, PhD, Inflammation, Repair and Development Section, National Heart and Lung Institute, Imperial College London, South Kensington Campus, Level 3, Sir Alexander Fleming Building, London SW7 2AZ, United Kingdom. E-mail: robert.snelgrove@imperial.ac.uk.

J Allergy Clin Immunol 2018;■■■:■■■-■■■.

0091-6749/\$36.00

© 2018 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaci.2018.06.009>

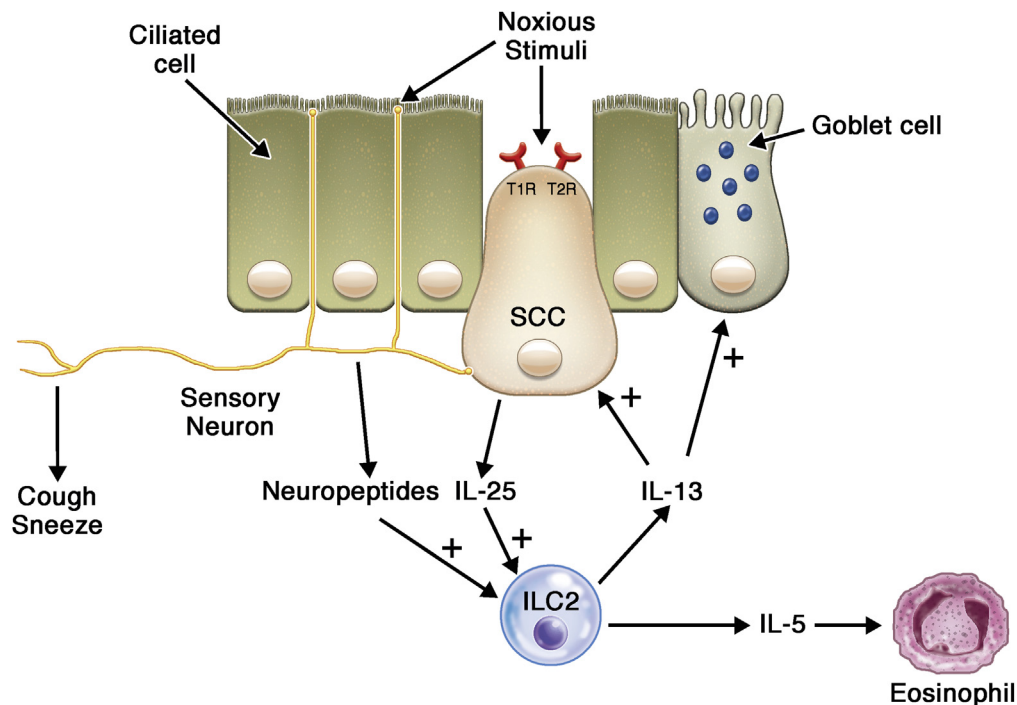


FIG 1. A putative SCC-sensory neuron network drives type 2 inflammation in the airways. In response to airway irritants, sensory neurons can directly or indirectly (through bitter taste receptor-expressing SCCs) be activated to promote reflexes, such as cough or sneeze. SCCs can also release IL-25, which, in combination with specific neuropeptides released from sensory neurons, will activate tissue-resident ILC2s. The ILC2s will in turn release IL-13, which feeds back to promote SCC expansion, as well as promoting goblet cell metaplasia and mucus release. Such a response is optimal for expulsion of noxious irritants, but an overzealous response could underlie the pathologic inflammation and remodeling of type 2 diseases.

perceived threat, which then function to drive ILC2 activation, proliferation, and type 2 cytokine production.⁹⁻¹¹ Thus a network of specialized epithelial cells and sensory neurons could potentially modulate ILC2 function through both IL-25 and neuropeptide release (Fig 1). Furthermore, the diverse array of noxious stimuli that trigger SCCs could in part rationalize how and why a type 2 response is initiated readily and orchestrated to diverse microbial and nonmicrobial stimuli and suggests an important role for cells that “taste” the environment in the induction and exacerbation of type 2 pathologies. In addition to CRSwNP, future studies should therefore look to determine the prevalence and functional significance of this SCC-IL-25 axis in patients with other diseases, such as allergic and nonallergic rhinitis and asthma, to ascertain whether this is a common fundamental pathway in the initiation of type 2 inflammation in distinct disease modalities.

Clinical trials targeting IL-33 and thymic stromal lymphopoietin pathways are ongoing for the treatment of CRSwNP, and in light of this and previous studies, there is an argument that IL-25 is also an attractive therapeutic target in patients with CRSwNP and of course other type 2 inflammatory diseases of the airways. More broadly, SCCs might represent a viable target in that they are seemingly fundamental early drivers of both type 2 inflammation and the sneezing, coughing, and apnea that are associated with chronic respiratory diseases and significantly compromise the patient's quality of life. A fuller understanding of the contribution of the bitter taste signaling pathway in defining SCC-IL-25 release, as well as trigeminal nerve-driven reflexes, might reveal pathways that can be manipulated for therapeutic gain.

REFERENCES

1. von Moltke J, Ji M, Liang HE, Locksley RM. Tuft-cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit. *Nature* 2016;529:221-5.
2. Gerbe F, Sidot E, Smyth DJ, Ohmoto M, Matsumoto I, Dardalhon V, et al. Intestinal epithelial tuft cells initiate type 2 mucosal immunity to helminth parasites. *Nature* 2016;529:226-30.
3. Howitt MR, Lavoie S, Michaud M, Blum AM, Tran SV, Weinstock JV, et al. Tuft cells, taste-chemosensory cells, orchestrate parasite type 2 immunity in the gut. *Science* 2016;351:1329-33.
4. Kohanski MA, Workman AD, Patel NN, Hung LY, Shtraks JP, Chen B, et al. Solitary chemosensory cells are a primary epithelial source of IL-25 in patients with chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol* 2018;142 XXX-XXX.
5. Tizzano M, Gulbransen BD, Vandenbeuch A, Clapp TR, Herman JP, Sibhatu HM, et al. Nasal chemosensory cells use bitter taste signaling to detect irritants and bacterial signals. *Proc Natl Acad Sci U S A* 2010;107:3210-5.
6. Shin HW, Kim DK, Park MH, Eun KM, Lee M, So D, et al. IL-25 as a novel therapeutic target in nasal polyps of patients with chronic rhinosinusitis. *J Allergy Clin Immunol* 2015;135:1476-85.e7.
7. Shaw JL, Fakhri S, Citardi MJ, Porter PC, Corry DB, Kheradmand F, et al. IL-33-responsive innate lymphoid cells are an important source of IL-13 in chronic rhinosinusitis with nasal polyps. *Am J Respir Crit Care Med* 2013; 188:432-9.
8. Miljkovic D, Bassiouni A, Cooksley C, Ou J, Hauben E, Wormald PJ, et al. Association between group 2 innate lymphoid cells enrichment, nasal polyps and allergy in chronic rhinosinusitis. *Allergy* 2014;69:1154-61.
9. Cardoso V, Chesne J, Ribeiro H, Garcia-Cassani B, Carvalho T, Bouchery T, et al. Neuronal regulation of type 2 innate lymphoid cells via neuromedin U. *Nature* 2017;549:277-81.
10. Klose CSN, Mahlakoiv T, Moeller JB, Rankin LC, Flamar AL, Kabata H, et al. The neuropeptide neuromedin U stimulates innate lymphoid cells and type 2 inflammation. *Nature* 2017;549:282-6.
11. Wallrapp A, Riesenfeld SJ, Burkett PR, Abdulnour RE, Nyman J, Dionne D, et al. The neuropeptide NMU amplifies ILC2-driven allergic lung inflammation. *Nature* 2017;549:351-6.