The Journal of Immunology

The Immune Function of Tuft Cells at Gut Mucosal Surfaces and Beyond

Hung-An Ting and Jakob von Moltke

J Immunol March 1, 2019, 202 (5) 1321-1329; DOI: https://doi.org/10.4049/jimmunol.1801069

Abstract

Tuft cells were first discovered in epithelial barriers decades ago, but their function remained unclear until recently. In the last 2 years, a series of studies has provided important advances that link tuft cells to infectious diseases and the host immune responses. Broadly, a model has emerged in which tuft cells use chemosensing to monitor their surroundings and translate environmental signals into effector functions that regulate immune responses in the underlying tissue. In this article, we review the current understand tuft cell immune function in the intestines, airways, and thymus. In particular, we discuss the role of tu in type 2 immunity, norovirus infection, and thymocyte development. Despite recent advances, many fundamental questions about the function of tuft cells in immunity remain to be answered.

Introduction

Epithelial cells (and indeed many other nonhematopoietic cells) are perhaps underappreciated by immunologists who focus on cells of the hematopoietic system, yet they make crucial contributions to immunity. Most notably, epithelia form the body's barrier between self and nonself and are, therefore, often the site of first encounter between the host and a foreign microbe or irritant. Although not as diverse as the

hematopoietic compartment, epithelial barriers are comprised of multiple cell lineages with both overlapping and distinct functions. Goblet cells, for example, are professional mucus-producing cells, whereas Paneth cells secrete high levels of antimicrobial peptides, and enteroendocrine cells secrete hormones and communicate with the nervous system. The role of tuft cells, in contrast, remained enigmatic for more than 60 years until a series of recent discoveries definitively linked tuft cells to immunity. In this review, we will focus on the immune function of tuft cells after a brief discussion of their development and markers.

Characteristics and distribution

Tuft cells were first discovered in rat trachea (1) and mouse glandular stomach (2) in 1956 and in human trachea in 1959 (3). The advent of electron microscopy had allowed for visualization of cellular morphology in unprecedented detail, and several investigators quickly noted the presence of a rare but distinctive lineage of epithelial cells, which they termed tuft, brush, caveolated, multivesicular, or fibrillovesicular cells (1, 4). As these cells appear to be very closely related across tissues, we will refer to them collectively as tuft cells. Morphologically, tuft cells are characterized by the following: 1) a "tuft" of long, blunt apical microvilli; 2) prominent actin, villin, and fimbrin rootlets that extend basally from the tips of the microvilli; and 3) abundant apical vesicles that form a tubulovesicular system. They are radiation-resistant epithelial cells (5) with a turnover rate equivalent to their surrounding epithelial cells, which is 3–5 days in the intestine (6–8) and 168–267 days in the trachea (9–11). With the exception of nascent tuft cells in intestinal crypts (12), tuft cells do not express the proliferation marker Ki67, indicating postmitotic status in both the steady-state (7, 12, 13) and during helminth infection (14).

In rodents, tuft cells have been identified in the digestive system [salivary glands (15), stomach (2), gall bladder and bile duct (16, 17), pancreatic duct (18), small intestine (19), cecum (20), and colon (21)], the respiratory system [nasal cavity (22), auditory tube (23), and trachea (1)], the urethra (24), and even in the thymus (25), a primary lymphoid organ. In rats, cells with tuft-like morphology have also been observed in the alveolar epithelium (26), but in mice, they have not been seen below the bronchial branch point. In humans, cells with tuft-like morphology were reported in the trachea (3), small intestine (27, 28), stomach (29, 30), gallbla (31), and in the alveoli of a 4-month-old patient with pneumonitis (32). As a rule, tuft cells are found in organs or tubes lined by a nonsquamous epithelium, but the thymus is a notable exception, and there are nonsquamous mucosal barriers where tuft cells have as yet not been described, such as the female reproductive tract.

Lineage specification

Although tuft cells are found in many tissues, their development and lineage specification has only been studied in detail in the small intestine, likely because the stem cells of the intestinal epithelium are among the best characterized and most prolific in the body (33). In homeostasis, these cells reside at the base of intestinal crypts, express the marker LGR5, and produce enough progeny to replace the entire intestinal epithelium in just 3–5 days (6). Lineage tracing has demonstrated that intestinal tuft cells are indeed derived

from LGR5$^+$ stem cells (7), but unlike all other epithelial cells, differentiated intestinal tuft cells continue to express *Lgr5* (34, 35).

Immediately above the LGR5$^+$ stem cell compartment is the transit amplifying zone, where uncommitted epithelial progenitors replicate and adopt their terminal fate. The first lineage branch point is regulated by a classical lateral inhibition model in which cells receiving a Notch signal upregulate Hairy and enhancer of split-1 (*Hes1*) and become enterocytes (36), whereas those providing a Notch ligand (e.g., Delta-like ligand 1 [DLL1]–expressing progenitors) retain potential to become all nonenterocyte lineages (goblet, enteroendocrine, Paneth, and tuft). Loss of Notch signaling induces atonal bHLH transcription factor 1 (*Atoh1*), which goblet, enteroendocrine, and Paneth cells all constitutively express. Accordingly, these cells are absent when *Atoh1* is deleted from epithelial stem cells (7, 12, 37). Mature tuft cells, in contrast, do not express *Atoh1*, and studies that deleted *Atoh1* from all intestinal epithelial cells reported conflicting results about the requirement of *Atoh1* in intestinal tuft cell development. Although tuft cells were absent in the small intestine of Villin-Cre^{Ert2} × Atoh1$^{f/f}$ mice (7), their numbers were normal or even increased in Rosa26-Cre^{Ert2} × Atoh1$^{f/f}$ (12), Lgr5-Cre^{Ert2} × Atoh1$^{f/f}$ (38), and Lrig-Cre^{Ert2} × Atoh1$^{f/f}$ (37) mice. Interestingly, colonic tuft cells, which were only studied in Lrig-Cre^{Ert2} × Atoh1$^{f/f}$ mice, did require *Atoh1*, suggesting distinct mechanisms of lineage specification in the small intestine and colon. Although some uncertainty remains, on balance, these studies suggest that a binary HES1/ATOH1 model does not fully explain the differentiation of intestinal epithelium.

Intestinal tuft cell development is not affected in the absence of the transcription factors neurogenin 3 (NEUROG3), SAM-pointed domain-containing ETS transcription factor (SPDEF), and sex-determining region Y-box 9 (SOX9), which are the lineage transcription factors that define enteroendocrine cells, goblet cells, and Paneth cells (7, 12). Instead, POU class 2 homeobox 3 (POU2F3) and growth factor–independent 1B (GFI1B) have been suggested as tuft cell–specific master regulators. All tuft cells express both markers constitutively (12, 39, 40), and tuft cells are entirely absent in *Pou2f3*$^{-/-}$ mice, whereas all other epithelial lineages appear normal, at least in the intestine (39). The status of tuft cells in the absence of *Gfi1b* has not been reported and it is unknown if either POU2F3 or GFI1B is sufficient to drive tuft cell differentiation. In the airway, tuft cells were shown to be derived from basal cells with rapid kinetics in lineage tracing experiments, but the p signals that specify the tuft cell lineage remain uncertain here as well (41).

The timing of tuft cell emergence during development also remains unclear. One study found that tuft cells appeared by mouse embryonic day 18.5 in developing intestine and stomach antrum (30); in other studies, tuft cells did not appear until after birth (42, 43). These studies all demonstrated that both gastric and intestinal tuft cell frequency remained very low before reaching adult-equivalent density after weaning (30, 42, 43), with similar frequency between the small intestine and the colon in unmanipulated mice (35). In contrast, tracheal tuft cells are present at adult frequency by at least day 5 postbirth (11). Overall there is much more to be learned about tuft cell lineage specification across diverse tissues, particularly how it can be regulated by immune signals in homeostasis and disease. IL-13 signaling in small intestinal stem cells, for example, can

induce tuft cell hyperplasia (14, 44, and discussed in detail below), but it is unclear whether this occurs in any other tissues.

Tuft cell heterogeneity

Although morphologically very similar, the developmental and functional equivalence of tuft cells in different tissues and even in different regions of the same tissue remains unclear. A list of tuft cell markers is included in Table I and we recently used bulk RNA sequencing of epithelial cell adhesion molecule (EPCAM)$^+$ IL-25$^+$ tuft cells from five different tissues to identify a core transcriptional signature that is shared by all tuft cells (45). In addition to *Il25*, this signature includes many of the markers listed in Table I, such as doublecortin-like kinase 1 (*Dclk1*), transient receptor potential cation channel subfamily M member 5 (*Trpm5*), PG endoperoxide synthase 1 (*Ptgs1*), *Pou2f3*, *Gfi1b*, and Sialic acid–binding Ig-like lectin F (*Siglecf*). Despite these shared features, RNA sequencing as well as immunostaining have also revealed significant inter- and intratissue diversity of tuft cells. For example, a recent study used multiplex immunofluorescence to demonstrate that individual DCLK1$^+$ tuft cells in the intestine express differential levels of markers such as acetylated tubulin (acTUB), SOX9, PTGS1 (COX1), and PTGS2 (COX2) (35). Tuft cell heterogeneity was also identified using single cell sequencing, which led to the classification of Tuft-1 and Tuft-2 subsets in both the airway and intestine (41, 46). In both tissues, expression of eicosanoid biosynthesis genes and *Ptprc* (also known as *Cd45*) is enriched in Tuft-2 cells. Intestinal Tuft-1 cells express a neuronal signature, whereas the tracheal Tuft-1 subset is associated with a taste transduction signature. In terms of cytokines, *Il25* is constitutively expressed in all tuft cells, whereas *Tslp* is detectable in both Tuft-1 and Tuft-2 cells of the trachea but only in Tuft-2 cells of the small intestine. In the trachea, there is also subset-specific skewing of transcription factors, with Tuft-1 cells enriched for *Pou2f3* and Tuft-2 cells for *Gfi1b*, but both genes remain detectable in all tuft cells. By bulk RNA sequencing (45), one key distinction between tuft cells from distinct tissues was the differential expression of surface receptors, suggesting that tuft cells have evolved to sense different ligands depending on their microenvironment. Whether the effector functions of tuft cells are also tissue-specific requires further investigation.

Table I.

Tuft cell biomarkers

Immune function of tuft cells in the intestine

Tuft–group 2 innate lymphoid cell immune circuit.

The initiation of type 1 immune responses, from innate immune sensing to priming of adaptive cells, is relatively well understood. By contrast, much less is known about how helminths, protists, and allergens trigger a type 2 response. Group 2 innate lymphoid cells (ILC2s) are the dominant early source of IL-5, IL-9, and IL-13 in numerous models of type 2 inflammation (47–51), and understanding how ILC2s are activated has, therefore, been of great interest. ILC2s lack an Ag receptor, and there is little evidence that they sense type 2 agonists directly. Instead, ILC2s integrate numerous host-derived activating signals, including cytokines (e.g.,

IL-33 and IL-25) (47, 52, 53), lipids (e.g., leukotrienes) (54–56), and neuronal peptides (e.g., vasoactive intestinal peptide and Neuromedin U) (48, 57–60). Current models propose that ILC2s use these signals to monitor the status of their surrounding tissue and become activated by disruptions in homeostasis (61).

In the intestine, the link between IL-25 and helminth-induced type 2 responses is well-established: IL-25 (53, 62, 63) and its downstream adaptor Act1 mediate type 2 immunity to promote worm expulsion (64). Furthermore, IL-25 is sufficient to activate ILC2s and promote worm expulsion independently of adaptive Th2 function (47, 63). But the physiologic cellular source of IL-25 remained elusive until recently. Using *Il25*-RFP reporter mice and immunohistochemistry, recent studies identified tuft cells as the dominant source of IL-25 in the small intestine both at homeostasis and during helminth infection (14, 39). Tuft cell–derived IL-25 helps to drive a feed-forward tuft–ILC2 signaling circuit in which ILC2s are activated to produce IL-5, -9, and -13, thereby promoting type 2 inflammation. IL-13 also signals in undifferentiated epithelial cells, skewing their lineage commitment toward tuft and goblet cells (14, 39, 44). Because of the rapid turnover of the intestinal epithelium, activation of the tuft–ILC2 circuit quickly results in pronounced tuft and goblet cell hyperplasia. The frequency of tuft cells, in particular, can increase more than 10-fold during helminth infection. This circuit can be activated exogenously by stimulating ILC2s with rIL-25 or rIL-33, or by giving rIL-13 to drive tuft cell hyperplasia directly in the intestinal epithelium. Removing components of the tuft–ILC2 circuit (e.g., *Pou2f3*$^{-/-}$, *Il25*$^{-/-}$, and *Il4Rα*$^{-/-}$) disrupts the intestinal type 2 response and leads to delayed clearance of the roundworm *Nippostrongylus brasiliensis* (14, 39, 65). Conversely, deleting the innate immune signaling inhibitor TNF-α–induced protein 3 (*Tnfaip3*, encoding A20) from ILC2s leads to chronic activation of the small intestinal tuft–ILC2 circuit driven by the constitutive expression of IL-25 in tuft cells (43). Model summarized in Fig. 1.

FIGURE 1.

Chemosensing by intestinal tuft cells regulates the tuft–ILC2 circuit. (**A**) Intestinal Tuft–ILC2 circuit. Tuft cells constitutively express *Il25*, which acts on ILC2s in the lamina propria to induce production of canonical type 2 cytokines IL-5, -9, and -13, which collectively drive all aspects of innate type 2 inflammation, including eosinophilia and intestinal remodeling. IL-13, in particular, signals in undifferentiated epithelial cells to bias their lineage commitment toward tuft and goblet cells, leading to hyperplasia of both cell types and driving the feed-forward tuft–ILC2 circuit. The circuit is amplified but yet unknown mechanisms when helminths or protists are sensed by tuft cells. Deletion of the signaling repressor A20 from ILC2s also amplifies the circuit and leads to chronic type 2 inflammation in the small intestine. (**B**) Chemosensing. Tuft cells sense succinate secreted from *Tritrichomonas* protists and, perhaps, also bacteria and helminths. Signaling through the G protein–coupled SUCNR1 induces an intracellular Ca^{2+} flux that opens the cation channel TRPM5, leading to influx of Na^{+} and depolarization of the cells. How cellular depolarization regulates tuft cell effector functions remains unknown but may include release of neurotransmitter (e.g., acetylcholine [Ach]) that acts on nearby neurons. Tuft cells also express the MNoV receptor CD300LF and are the host reservoir for chronic infection by the CR6 strain of norovirus. It is not clear if and how tuft cells sense this infection.

Tuft cells are also found constitutively in the gall bladder, pancreatic ducts, cecum, and colon, where they express many of the same markers (e.g., DCLK1, choline acetyltransferase [CHAT], and TRPM5) as in the small intestine. An immune function has not, however, been reported for any of these cells. In fact, all evidence so far suggests that the tuft–ILC2 circuit does not operate in these tissues. For example, deleting A20 from ILC2s spontaneously activates the tuft–ILC2 circuit in the small intestine, but there is no evidence of type 2 inflammation in any other intestinal tissues (43). Further, systemic delivery of rIL-4 drives tuft cell hyperplasia only in the small intestine (J. von Moltke and R.M. Locksley, unpublished observations). It may be that tuft cells and ILC2s still communicate outside the small intestine but that IL-4/13 signaling in epithelial stem cells at these sites does not induce tuft cell hyperplasia. Small and transient changes in tuft cell frequency have been noted in the colon when germ-free mice are colonized with bacteria (35), but the mechanism for these fluctuations remains unknown.

In young, unmanipulated mice, ILC2s are the dominant IL-25R–expressing and IL-13–producing tissue-resident cells and are therefore critical for rapid (7–10 day) clearance of the rodent roundworm *N. brasiliensis*. In chronic infection settings (e.g., with the helminth *Heligmosomoides polygyrus*) or once immune memory is established, other sources of IL-13 are activated and can likely substitute for ILC2s in the circuit. In fact, the connections between tuft cells and adaptive immunity remain completely unexplored. In addition, several details of the innate tuft–ILC2 circuit require further examination. In particular, how is the circuit regulated if IL-25 expression is constitutive, and what do tuft cells do besides secrete IL-25? Besides cytokines, tuft cells also express enzymes for eicosanoid biosynthesis, such as *Cox-1*, *Cox-2*, 5-lipoxygenase (*Alox5*), and

hematopoietic PG-D synthase (*Hpgds*) (7, 14, 46, 66–68). How eicosanoid biosynthesis is regulated in tuft cells and the physiologic function of tuft cell–derived eicosanoids remains unknown.

Tuft cell chemosensing.

Soon after the link between tuft cells and helminth infection was established, another landmark study revealed that the tuft–ILC2 circuit is also activated by intestinal colonization with *Tritrichomonas*, a genus of protists found in the commensal flora of many mouse vivariums (44). This study also provided the first functional evidence of a link between chemosensing by tuft cells and type 2 immunity.

Immune cells and intestinal epithelial cells are known to sense microbially-derived molecular patterns with pattern recognition receptors, such as TLR, to initiate type 1 immunity, but the molecular stimuli and the cell type(s) that drive type 2 responses are still elusive. A sensing function has long been hypothesized for tuft cells, and immunostaining provided the first clues that a chemosensing pathway previously characterized in taste transduction might also be active in tuft cells (67, 69–71). In taste receptor cells, signaling through canonical G protein–coupled taste receptors activates a specialized G α subunit known as α-gustducin (GNAT3), which in turn initiates intracellular calcium flux via phospholipase C β 2 (PLCB2) (72). The rise in Ca^{2+} opens the cell surface cation channel TRPM5, leading to depolarization of taste cells. When the first complete transcriptome analysis of intestinal tuft cells was completed in 2008, it confirmed that all components of the pathway, except canonical taste receptors, are indeed highly and selectively expressed in tuft cells (66).

Tuft cells are ideally positioned to act as immune sentinels by monitoring the intestinal lumen and transmitting signals to immune cells in the underlying tissue. Howitt et al. (44) provided the first direct evidence for such a function, by demonstrating that *Trpm5*$^{-/-}$ and *Gnat3*$^{-/-}$ mice fail to induce tuft cell hyperplasia when colonized with *Tritrichomonas*. Immune responses to the helminths *N. brasiliensis* and *H. polygyrus* are also impaired in *Trpm5*$^{-/-}$ mice (44), but tuft cell hyperplasia occurs normally in *Gnat3*$^{-/-}$ mice colonized with *N. brasiliensis*, suggesting distinct sensing mechanisms for helminths and protists (45).

The lack of canonical taste receptor expression in intestinal tuft cells suggested the hypothesis that ot protein–coupled receptor(s) may be specifically enriched on tuft cells to "sense" protists and helminth Indeed, the extracellular succinate receptor 1 (SUCNR1) was recently identified to be selectively expressed in both TRPM5^{+} and IL-25^{+} small intestinal tuft cells (45, 66, 73). Remarkably, providing succinate in the drinking water of mice is sufficient to drive tuft cell hyperplasia in a *Sucnr1*-, *Il25*-, and *Trpm5*-dependent manner (45, 73). Succinate treatment also induces other hallmarks of type 2 responses, such as goblet cell hyperplasia, eosinophilia, and IL-13 production by ILC2s (43, 45). Further, the activation of ILC2s by succinate is *Il25*-, *Trpm5*-, and *Pou2f3*-dependent (43, 45, 73). Succinate is therefore the first ligand identified for intestinal tuft cells and one of the only known innate immune ligands that is sufficient to activate type 2 inflammation.

Succinate is an intermediate of the citric acid cycle and is normally sequestered inside host cells. Many microbial pathogens and commensals, in contrast, have evolved diverse fermentative metabolic pathways to

thrive in the nutrient-rich but oxygen-poor intestinal lumen, and these pathways frequently result in production and secretion of succinate (74). Succinate is detectable in the supernatants of in vitro–cultured *N. brasiliensis* and *Tritrichomonas* and in the cecum of mice monocolonized with *Tritrichomonas*. Accordingly, the detection of *Tritrichomonas* by tuft cells is entirely SUCNR1-dependent (43, 45). By contrast, the immune response to *N. brasiliensis* is intact in *Sucnr1*$^{-/-}$ mice (45, 73), demonstrating that SUCNR1 signaling is absent or redundant during helminth infection and underscoring the differences between sensing of protists and helminths that was suggested by experiments using *Gnat3*$^{-/-}$ mice. There is also evidence that bacterial dysbiosis leads to SUCNR1-dependent tuft cell hyperplasia, although it is not clear whether this occurs physiologically (73). Together, these studies identify a specific metabolite that selectively activates the tuft–ILC2 circuit and define a paradigm in which the intestinal type 2 immune system monitors microbial metabolism. Tuft cells also express another potential metabolite sensor [e.g. free fatty acid receptor 3 (FFAR3) (45, 46)], but a function for this receptor has remained elusive.

The seemingly intact immune response to *N. brasiliensis* in *Gnat3*$^{-/-}$ and *Sucnr1*$^{-/-}$ mice suggests that there is at least one other sensor upstream of TRPM5 that detects helminth infection. There are also questions remaining about the mechanisms of chemosensing by tuft cells in other tissues. The detection of succinate also warrants further investigation. In particular, the benefits of sensing *Tritrichomonas*-derived succinate are unclear because these protists are not eliminated or even reduced in number by the type 2 immune response (45). Given that most protists and helminths have evolved to establish chronic colonization, their sensing by the immune system may, therefore, be linked principally to host adaptation and tolerance. In support of this idea, activation of the tuft–ILC2 circuit was recently shown to drive small intestinal lengthening (43). Because tuft and goblet cell hyperplasia lead to a decreased frequency of absorptive enterocytes, this intestinal lengthening may help to maintain the absorptive capacity of the intestine. Indeed, there is no overt loss of fitness or decrease in caloric uptake associated with chronic activation of the tuft–ILC2 circuit (43).

Tuft cells and norovirus.

Human norovirus is the leading cause of gastroenteritis outbreaks worldwide, and the acute phase of disease can be followed by weeks or months of viral shedding in the stool (75), suggesting a site of vir... persistence in the host. Murine norovirus (MNoV) is even more persistent, with some strains establishing chronic infection, but the cellular tropism in vivo remained unclear until recently. In 2017, immunostaining of nonstructural norovirus proteins demonstrated that a rare population of EPCAM^{+} cells in the small intestine and colon serve as the exclusive viral reservoir in mice infected with MNoV^{CR6} (76). These cells were soon identified to be tuft cells, which express high levels of the MNoV receptor CD300LF (5). Accordingly, mice were resistant to infection with MNoV^{CR6} when tuft cells were absent or decreased, whereas viral titers were enhanced in any context where tuft cell numbers were increased, such as helminth infection or treatment with rIL-25. In contrast, the nonpersistent strain MNoV^{CW3} was unable to infect intestinal epithelial cells (5, 76). Whether human norovirus and/or other enteric viruses also infect tuft cells remains to be determined. It also

remains unclear why norovirus would target tuft cells for infections. Perhaps the unique cell biology of tuft cells is important for viral replication, or tuft cells represent an immune-privileged site.

Immune function beyond the intestine

Airway tuft cells.

Although often referred to as brush cells, a population of airway epithelial cells has been identified in the murine and human trachea that share the unique morphology and transcriptional signature of intestinal tuft cells (10, 41, 45, 77). Another very closely related cellular lineage, termed solitary chemosensory cells (SCC), has also been identified in the nasal epithelium of mice and humans (22, 71, 78, 79), but its precise relationship to tuft cells has not yet been established. Unlike intestinal tuft cells, both tuft cells and SCCs of the airways express type II taste receptors (T2Rs, also known as bitter taste receptors) in humans (78) and mice (22, 80), and bitter taste receptor polymorphisms correlate with Gram-negative bacterial infection in humans (81). Type II taste receptors have been linked to regulation of both tissue physiology and immune responses. For example, denatonium, a potent bitter taste receptor ligand, can act on tuft cells to regulate respiration rate (82), nasal neurogenic inflammation (83), and allergic asthma induced by OVA and house dust mites in mice (84). The bitter receptors on SCCs are reported to detect acyl-homoserine lactones, which are produced by Gram-negative bacteria (e.g., *Pseudomonas aeruginosa*) (85) to indicate population density (79, 86). Moreover, bitter taste receptors activate calcium flux in nasal SCCs to stimulate antimicrobial peptide secretion from surrounding epithelial cells and promote killing of *P. aeruginosa*, methicillin-resistant *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *S. epidermis* in human sinonasal tissue (79, 87). SCCs also express canonical sweet taste receptors (T1R2/3), but their activation suppresses calcium flux and bitter taste receptor–induced antimicrobial responses (87). T1R2/3 mediate sensing of glucose and bacterial D-amino acids in SCCs, leading to reduced antimicrobial peptide secretion (β-defensin) (87, 88). Clinically, there are elevated glucose and amino acid concentrations in chronic rhinosinusitis patients and colonized fibrosis patients, respectively (87, 89). Together, these important studies suggest that SCCs and, perhaps, airway tuft cells use chemosensory machinery to "taste" the upper respiratory tract environment and regulate innate imm

Whether airway tuft cells and SCCs are also integrated into tuft–ILC2 circuits and how this might alter type 2 immune responses remains unknown. Manipulation of IL-25 by intranasal administration, systemic blockade, or genetic deficiency all regulates lung type 2 airway inflammation (63, 90–92), but the expression of IL-17RB (a subunit of IL-25R) is much lower on lung ILC2s than in the intestine, even with IL-25 injection (93). Furthermore, the restriction of tuft cells to the upper airways in mice is confounding when considering inflammatory responses in the distal lung (10). In humans, SCCs are the major source of IL-25 in patients with chronic rhinosinusitis (94, 95), and ILC2 numbers were elevated in nasal polyps from chronic rhinosinusitis patients (95). These results support the existence of a tuft–ILC2 circuit in the human nasal cavity. There were also human case reports suggesting that brush (tuft) cell numbers are altered in immotile cilia syndrome (96) and interstitial pneumonitis (32). Together, future studies may further investigate the expression, detection

mechanism, and corresponding immune function of taste receptors and other novel G protein receptors on airway tuft cells, especially in the upper versus lower respiratory tract.

Thymic tuft cells.

In all of the examples discussed so far, tuft cells were found in the nonsquamous epithelium of hollow tissues. Therefore, it was surprising when cells with tuft-like morphology and expression of *Gnat3, Plcb2*, and *Chat* were identified in the thymic medulla (25).

More recently, RNA sequencing and careful phenotyping confirmed that these cells are indeed bona fide tuft cells and that they compose 3 ~ 10% of medullary thymic epithelial cells (mTEC) in murine thymus and ~3.5% of mTEC in human thymus (97, 98). Based on single cell sequencing, tuft cells comprise mTEC group IV, which is molecularly distinct from other mTECs but closely related to intestinal tuft cells, with *Dclk1*, *Sox9*, *Trpm5*, *Il25,* and *Pou2f3* all being expressed (97, 98). There are, however, also important differences between thymic tuft cells and those of other tissues; most notably, IL-25$^+$ thymic tuft cells express MHC class II, suggesting an Ag-presenting function (98). Thymic tuft cells also express a diversity of canonical taste receptors, which have been described in airway tuft cells but appear to be largely absent in intestinal tuft cells (45). As in other tissues, thymic tuft cell development requires *Pou2f3* (98, 97).

Functionally, thymic tuft cells support TCRβ^{int} CD1d$^+$ IL-4$^+$ invariant NKT2 thymocytes and EOMES$^+$ CD8 thymocytes in an *Il25-, Pou2f3-*, and *Trpm5*-dependent manner, although why chemosensing would be required for this function is completely unclear (96). The frequency of thymic Lin$^-$ TCR$^-$ CD127$^+$ GATA3$^+$ ILC2s is increased in the absence of tuft cells, but the functional significance of this remains unknown (97). Neither *Pou2f3* nor *Trpm5* deficiency impacted CD4$^-$CD8$^-$, CD4$^+$CD8$^+$, CD4 single-positive T cells, or CD8 single-positive T cells numbers in the thymus (97, 98). In sum, thymic tuft cells are a distinct population of mTECs that regulate the frequency of certain thymocyte subsets. Their "sensing" mechanism by taste receptors, their ontogeny, their relationship to Ag presentation, and their function in immune tolerance remain enigmatic.

Tuft cells and neurons?

In addition to the outstanding questions already highlighted throughout this review, there is significant interest in the possibility that tuft cells might communicate with neurons, a finding which could provide mechanistic insight for numerous recent studies that have broadly linked the nervous and immune systems and specifically implicated neuronal signaling in type 2 inflammation (58, 99). In this context, it is notable that tuft cells in all tissues express CHAT (45, 67, 82, 83,), the enzyme required for synthesis of the neurotransmitter acetylcholine. To date, a link between tuft cells and neurons has been best characterized in the airway. Although tuft cells and neurons do not form synaptic connections, they have been imaged in close proximity in the airway (82, 83, 100), and some of those neurons express acetylcholine receptors (83, 101). Accordingly, the airway inflammation induced by stimulating SCCs requires *Trpm5* and acetylcholine (83). For the most part, however, tuft–neuron interactions have not been linked directly to immunity. For example,

changes in respiratory rate induced by bitter substances are absent in *Trpm5*$^{-/-}$ mice and in mice where the airway epithelium has been abraded, suggesting that chemosensing by tuft cells regulates smooth muscle activity (79, 82), presumably via neuronal signaling. Similarly, bitter substances induce acetylcholine release from urethral tuft cells and cause contraction of the bladder detrusor muscle when delivered in vivo (102). Whether these tuft–neuron interactions in the airway and urethra represent mechanisms of avoidance and/or flushing that provide immune protection has not been tested.

The link between tuft cells and neurons in the intestine remains much less clear, given different findings regarding tuft–neuron proximity (67, 70, 103). Intriguingly, intestinal tuft cells are positive for both CHAT and the neuropeptide β-endorphin (7, 67), and coculture of neurons and intestinal organoids supports the differentiation of tuft cells (38). Interactions between tuft cells and the enteric nervous system, if verified, might serve to expand the sensing capacity of the nervous system while also broadly distributing signals initiated in tuft cells.

Conclusions

After decades of pioneering work provided the first hints of a chemosensing pathway in tuft cells and suggested a role for tuft cells in response to bacterial colonization in the airways, the last 2 years brought a series of breakthroughs that definitively implicated tuft cells in immune sensing and regulation. It is now clear that tuft cells are a critical component of the type 2 immune response, provide a reservoir for chronic norovirus infection, and contribute to thymic function. Although it has been exciting to find an immune role for the previously enigmatic tuft cell lineage, we speculate that this does not represent their most evolutionarily ancient function. Undoubtedly, tuft cells have been critically shaped by coevolution with helminths, protists, norovirus, and perhaps other microbes, but just as goblet cells produce mucus at homeostasis to support epithelial function and can be hyperactivated to promote helminth expulsion, we propose that tuft cells first evolved epithelial effector functions that were later useful for immunity and/or pathogenic exploitation. In this context, it is intriguing that tuft cells have been implicated in airway contraction, epithelial regeneration, DNA damage repair (18, 68, 104), and tumorigenesis (38, 105–107). If correct, our hypothesis suggests that understanding the unique cell biology of tuft cells and their role in the absence of infection will also advance our understanding of tuft cells in immunity.

Disclosures

The authors have no financial conflicts of interest.

Acknowledgments

We thank T. Billipp, J. McGinty, and M. Fontana for reading the manuscript and for helpful discussions. J.v.M. is a Damon Runyon–Dale Frey Breakthrough Scientist and a Searle Scholar.

Footnotes

- This work was supported by National Institutes of Health 1DP2 OD024087 (to J.v.M.) and the University of Washington.

- Abbreviations used in this article:

Atoh1
atonal bHLH transcription factor 1

CHAT
choline acetyltransferase

Dclk1
doublecortin-like kinase 1

GFI1B
growth factor–independent 1B

ILC2
group 2 innate lymphoid cell

MNoV
murine norovirus

mTEC
medullary thymic epithelial cell

PLCB2
phospholipase C β 2

POU2F3
POU class 2 homeobox 3

Ptgs1
PG endoperoxide synthase 1

SCC
solitary chemosensory cell

SUCNR1
succinate receptor 1

Trpm5
transient receptor potential cation channel subfamily M member 5.

Received August 1, 2018.

Accepted September 21, 2018.

References

1. Rhodin, J., T. Dalhamn. 1956. Electron microscopy of the tracheal ciliated mucosa in rat. *Z. Zellforsch. Mikrosk. Anat. Vienna Austria* **44**: 345–412. Google Scholar

2. Jarvi, O., O. Keyrilainen. 1956. On the cellular structures of the epithelial invasions in the glandular stomach of mice caused by intramural application of 20-methylcholantren. *Acta Pathol Microbiol Scand Suppl* **39**(Suppl. 111): 72–73. PubMed Google Scholar

3. Rhodin, J. 1959. LXVII ultrastructure of the tracheal ciliated mucosa in rat and man. *Ann. Otol. Rhinol. Laryngol.* **68**: 964–974. CrossRef Google Scholar

4. Reid, L., B. Meyrick, V. B. Antony, L.-Y. Chang, J. D. Crapo, H. Y. Reynolds. 2005. The mysterious pulmonary brush cell: a cell in search of a function. *Am. J. Respir. Crit. Care Med.* **172**: 136–139. CrossRef PubMed Google Scholar

5. Wilen, C. B., S. Lee, L. L. Hsieh, R. C. Orchard, C. Desai, B. L. Hykes Jr.., M. R. McAllaster, D. R. Balce, T. Feehley, J. R. Brestoff, et al. 2018. Tropism for tuft cells determines immune promotion of norovirus pathogenesis. *Science* **360**: 204–208. Abstract/FREE Full Text Google Scholar

6. Barker, N. 2014. Adult intestinal stem cells: critical drivers of epithelial homeostasis and regeneration. *Nat. Rev. Mol. Cell Biol.* **15**: 19–33. CrossRef PubMed Google Scholar

7. Gerbe, F., J. H. van Es, L. Makrini, B. Brulin, G. Mellitzer, S. Robine, B. Romagnolo, N. F. Shroyer, J.-F. Bourgaux, C. Pignodel, et al. 2011. Distinct ATOH1 and Neurog3 requirements define tuft cells as a new secretory cell type in the intestinal epithelium. *J. Cell Biol.* **192**: 767–780. Abstract/FREE Full Text Google Scholar

8. Tsubouchi, S., C. P. Leblond. 1979. Migration and turnover of entero-endocrine and caveolated cells in the epithelium of the descending colon, as shown by radioautography after continuous infusion of 3H-thymidine into mice. *Am. J. Anat.* **156**: 431–451. CrossRef PubMed Google Scholar

9. Basbaum, C., B. Jany. 1990. Plasticity in the airway epithelium. *Am. J. Physiol.* **259**: L38–L46. Google Scholar

10. Krasteva, G., W. Kummer. 2012. "Tasting" the airway lining fluid. *Histochem. Cell Biol.* **138**: 365–383. CrossRef Google Scholar

11. Saunders, C. J., S. D. Reynolds, T. E. Finger. 2013. Chemosensory brush cells of the trachea. A stable population in a dynamic epithelium. *Am. J. Respir. Cell Mol. Biol.* **49**: 190–196. CrossRef PubMed Google Scholar

12. Bjerknes, M., C. Khandanpour, T. Möröy, T. Fujiyama, M. Hoshino, T. J. Klisch, Q. Ding, L. Gan, J. Wang, M. G. Martín, H. Cheng. 2012. Origin of the brush cell lineage in the mouse intestinal epithelium. *Dev. Biol.* **362**: 194–218. CrossRef PubMed Google Scholar

13. Nakanishi, Y., H. Seno, A. Fukuoka, T. Ueo, Y. Yamaga, T. Maruno, N. Nakanishi, K. Kanda, H. Komekado, M. Kawada, et al. 2013. Dclk1 distinguishes between tumor and normal stem cells in the intestine. *Nat. Genet.* **45**: 98–103. CrossRef PubMed Google Scholar

14. von Moltke, J., M. Ji, H.-E. Liang, R. M. Locksley. 2016. Tuft-cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit. *Nature* **529**: 221–225. CrossRef PubMed Google Scholar

15. Sato, A., S. Miyoshi. 1988. Ultrastructure of the main excretory duct epithelia of the rat parotid and submandibular glands with a review of the literature. *Anat. Rec.* **220**: 239–251. CrossRef PubMed Google Scholar

16. Luciano, L., M. Castellucci, E. Reale. 1981. The brush cells of the common bile duct of the rat. This section, freeze-fracture and scanning electron microscopy. *Cell Tissue Res.* **218**: 403–420. PubMed Google Scholar

17. Nevalainen, T. J. 1977. Ultrastructural characteristics of tuft cells in mouse gallbladder epithelium. *Acta Anat. (Basel)* **98**: 210–220. PubMed Google Scholar

18. Bailey, J. M., J. Alsina, Z. A. Rasheed, F. M. McAllister, Y.-Y. Fu, R. Plentz, H. Zhang, P. J. Pasricha, N. Bardeesy, W. Matsui, et al. 2014. DCLK1 marks a morphologically distinct subpopulation of cells with stem cell properties in preinvasive pancreatic cancer. *Gastroenterology* **146**: 245–256. CrossRef PubMed Google Scholar

19. Isomaki, A. 1962. Electron microscopic observations on a special cell type in gastro-intestinal epithelium of some laboratory animals. *Acta Pathol. Microbiol. Scand.* **154**: 115–118. Google Scholar

20. Okamoto, K., K. Hanazaki, T. Akimori, T. Okabayashi, T. Okada, M. Kobayashi, T. Ogata. 2008. Immunohistochemical and electron microscopic characterization of brush cells of the rat cecum. *Med. Mol. Morphol.* **41**: 145–150. CrossRef PubMed Google Scholar

21. Silva, D. G. 1966. The fine structure of multivesicular cells with large microvilli in the epithelium of the mouse colon. *J. Ultrastruct. Res.* **16**: 693–705. PubMed Google Scholar

22. Finger, T. E., B. Böttger, A. Hansen, K. T. Anderson, H. Alimohammadi, W. L. Silver. 2003. Solitary chemoreceptor cells in the nasal cavity serve as sentinels of respiration. *Proc. Natl. Acad. Sci. USA* **100**: 8981–8986. Abstract/FREE Full Text Google Scholar

23. Krasteva, G., P. Hartmann, T. Papadakis, M. Bodenbenner, L. Wessels, E. Weihe, B. Schütz, A. C. Langheinrich, V. Chubanov, T. Gudermann, et al. 2012. Cholinergic chemosensory cells in the auditory tube. *Histochem. Cell Biol.* **137**: 483–497. CrossRef PubMed Google Scholar

24. Deckmann, K., G. Krasteva-Christ, A. Rafiq, C. Herden, J. Wichmann, S. Knauf, C. Nassenstein, C. G. Grevelding, A. Dorresteijn, V. Chubanov, et al. 2015. Cholinergic urethral brush cells are widespread throughout placental mammals. *Int. Immunopharmacol.* **29**: 51–56. Google Scholar

25. Panneck, A. R., A. Rafiq, B. Schütz, A. Soultanova, K. Deckmann, V. Chubanov, T. Gudermann, E. Weihe, G. Kras Christ, V. Grau, et al. 2014. Cholinergic epithelial cell with chemosensory traits in murine thymic medulla. *Cell T* **358**: 737–748. CrossRef Google Scholar

26. Kasper, M., D. Höfer, J. Woodcock-Mitchell, A. Migheli, A. Attanasio, T. Rudolf, M. Müller, D. Drenckhahn. 1994. Colocalization of cytokeratin 18 and villin in type III alveolar cells (brush cells) of the rat lung. *Histochemistry* **101**: 57–62. CrossRef PubMed Google Scholar

27. Morroni, M., A. M. Cangiotti, S. Cinti. 2007. Brush cells in the human duodenojejunal junction: an ultrastructural study. *J. Anat.* **211**: 125–131. CrossRef PubMed Google Scholar

28. Moxey, P. C., J. S. Trier. 1978. Specialized cell types in the human fetal small intestine. *Anat. Rec.* **191**: 269–285. CrossRef PubMed Google Scholar

29. Johnson, F. R., B. A. Young. 1968. Undifferentiated cells in gastric mucosa. *J. Anat.* **102**: 541–551. PubMed Google Scholar

30. ↵Saqui-Salces, M., T. M. Keeley, A. S. Grosse, X. T. Qiao, M. El-Zaatari, D. L. Gumucio, L. C. Samuelson, J. L. Merchant. 2011. Gastric tuft cells express DCLK1 and are expanded in hyperplasia. *Histochem. Cell Biol.* **136**: 191–204. CrossRef PubMed Google Scholar

31. ↵Gilloteaux, J., B. Pomerants, T. R. Kelly. 1989. Human gallbladder mucosa ultrastructure: evidence of intraepithelial nerve structures. *Am. J. Anat.* **184**: 321–333. PubMed Google Scholar

32. ↵DiMaio, M. F., R. Dische, R. E. Gordon, M. Kattan. 1988. Alveolar brush cells in an infant with desquamative interstitial pneumonitis. *Pediatr. Pulmonol.* **4**: 185–191. PubMed Google Scholar

33. ↵Clevers, H. 2013. The intestinal crypt, a prototype stem cell compartment. *Cell* **154**: 274–284. CrossRef PubMed Google Scholar

34. ↵Itzkovitz, S., A. Lyubimova, I. C. Blat, M. Maynard, J. van Es, J. Lees, T. Jacks, H. Clevers, A. van Oudenaarden. 2011. Single-molecule transcript counting of stem-cell markers in the mouse intestine. *Nat. Cell Biol.* **14**: 106–114. CrossRef PubMed Google Scholar

35. ↵McKinley, E. T., Y. Sui, Y. Al-Kofahi, B. A. Millis, M. J. Tyska, J. T. Roland, A. Santamaria-Pang, C. L. Ohland, C. Jobin, J. L. Franklin, et al. 2017. Optimized multiplex immunofluorescence single-cell analysis reveals tuft cell heterogeneity. *JCI Insight* **2**: 93487. Google Scholar

36. ↵Jensen, J., E. E. Pedersen, P. Galante, J. Hald, R. S. Heller, M. Ishibashi, R. Kageyama, F. Guillemot, P. Serup, O. D. Madsen. 2000. Control of endodermal endocrine development by Hes-1. *Nat. Genet.* **24**: 36–44. CrossRef PubMed Google Scholar

37. ↵Herring, C. A., A. Banerjee, E. T. McKinley, A. J. Simmons, J. Ping, J. T. Roland, J. L. Franklin, Q. Liu, M. J. Gerdes, R. J. Coffey, K. S. Lau. 2018. Unsupervised trajectory analysis of single-cell RNA-seq and imaging data reveals alternative tuft cell origins in the gut. *Cell Syst.* **6**: 37–51.e9. Google Scholar

38. ↵Westphalen, C. B., S. Asfaha, Y. Hayakawa, Y. Takemoto, D. J. Lukin, A. H. Nuber, A. Brandtner, W. Setlik, H. Remotti, A. Muley, et al. 2014. Long-lived intestinal tuft cells serve as colon cancer-initiating cells. *J. Clin. Invest.* **124**: 1283–1295. CrossRef PubMed Google Scholar

39. ↵Gerbe, F., E. Sidot, D. J. Smyth, M. Ohmoto, I. Matsumoto, V. Dardalhon, P. Cesses, L. Garnier, M. Pouzolles, B. Brulin, et al. 2016. Intestinal epithelial tuft cells initiate type 2 mucosal immunity to helminth parasites. *Nature* **529**: 226–
CrossRef PubMed Google Scholar

40. ↵Yamashita, J., M. Ohmoto, T. Yamaguchi, I. Matsumoto, J. Hirota. 2017. Skn-1a/Pou2f3 functions as a master regulator to generate Trpm5-expressing chemosensory cells in mice. *PLoS One* **12**: e0189340. Google Scholar

41. ↵Montoro, D. T., A. L. Haber, M. Biton, V. Vinarsky, B. Lin, S. E. Birket, F. Yuan, S. Chen, H. M. Leung, J. Villoria, et al. 2018. A revised airway epithelial hierarchy includes CFTR-expressing ionocytes. *Nature* **560**: 319–324. CrossRef Google Scholar

42. ↵Gerbe, F., C. Legraverend, P. Jay. 2012. The intestinal epithelium tuft cells: specification and function. *Cell. Mol. Life Sci.* **69**: 2907–2917. CrossRef PubMed Google Scholar

43. ↵Schneider, C., C. E. O'Leary, J. von Moltke, H.-E. Liang, Q. Y. Ang, P. J. Turnbaugh, S. Radhakrishnan, M. Pellizzon, A. Ma, R. M. Locksley. 2018. A metabolite-triggered tuft cell-ILC2 circuit drives small intestinal remodeling. *Cell* **174**: 271–284.e14. Google Scholar

44. ↵Howitt, M. R., S. Lavoie, M. Michaud, A. M. Blum, S. V. Tran, J. V. Weinstock, C. A. Gallini, K. Redding, R. F. Margolskee, L. C. Osborne, et al. 2016. Tuft cells, taste-chemosensory cells, orchestrate parasite type 2 immunity in the gut. *Science* **351**: 1329–1333. Abstract/FREE Full Text Google Scholar

45. ↵Nadjsombati, M. S., J. W. McGinty, M. R. Lyons-Cohen, J. B. Jaffe, L. DiPeso, C. Schneider, C. N. Miller, J. L. Pollack, G. A. Nagana Gowda, M. F. Fontana, et al. 2018. Detection of succinate by intestinal tuft cells triggers a type 2 innate immune circuit. *Immunity* **49**: 33–41.e7. Google Scholar

46. ↵Haber, A. L., M. Biton, N. Rogel, R. H. Herbst, K. Shekhar, C. Smillie, G. Burgin, T. M. Delorey, M. R. Howitt, Y. Katz, et al. 2017. A single-cell survey of the small intestinal epithelium. *Nature* **551**: 333–339. CrossRef PubMed Google Scholar

47. ↵Price, A. E., H.-E. Liang, B. M. Sullivan, R. L. Reinhardt, C. J. Eisley, D. J. Erle, R. M. Locksley. 2010. Systemically dispersed innate IL-13-expressing cells in type 2 immunity. *Proc. Natl. Acad. Sci. USA* **107**: 11489–11494. Abstract/FREE Full Text Google Scholar

48. ↵Nussbaum, J. C., S. J. Van Dyken, J. von Moltke, L. E. Cheng, A. Mohapatra, A. B. Molofsky, E. E. Thornton, M. F. Krummel, A. Chawla, H.-E. Liang, R. M. Locksley. 2013. Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature* **502**: 245–248. CrossRef PubMed Google Scholar

49. Mohapatra, A., S. J. Van Dyken, C. Schneider, J. C. Nussbaum, H.-E. Liang, R. M. Locksley. 2016. Group 2 innate lymphoid cells utilize the IRF4-IL-9 module to coordinate epithelial cell maintenance of lung homeostasis. *Mucosal Immunol.* **9**: 275–286. CrossRef PubMed Google Scholar

50. Matsuki, A., H. Takatori, S. Makita, M. Yokota, T. Tamachi, A. Suto, K. Suzuki, K. Hirose, H. Nakajima. 2017. T-bet inhibits innate lymphoid cell-mediated eosinophilic airway inflammation by suppressing IL-9 production. *J. Allergy Clin. Immunol.* **139**: 1355–1367.e6. Google Scholar

51. ↵Halim, T. Y. F. 2016. Group 2 innate lymphoid cells in disease. *Int. Immunol.* **28**: 13–22. CrossRef PubMed Google Scholar

52. ↵Moro, K., T. Yamada, M. Tanabe, T. Takeuchi, T. Ikawa, H. Kawamoto, J. Furusawa, M. Ohtani, H. Fujii, S. Koyasu. 2010. Innate production of T(H)2 cytokines by adipose tissue-associated c-Kit(+)Sca-1(+) lymphoid cells. *Nature* **463**: 540–544. CrossRef PubMed Google Scholar

53. ↵Neill, D. R., S. H. Wong, A. Bellosi, R. J. Flynn, M. Daly, T. K. A. Langford, C. Bucks, C. M. Kane, P. G. Fallon, R. Pannell, et al. 2010. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. *Nature* **464**: 1367–1 CrossRef PubMed Google Scholar

54. ↵Doherty, T. A., N. Khorram, S. Lund, A. K. Mehta, M. Croft, D. H. Broide. 2013. Lung type 2 innate lymphoid cells express cysteinyl leukotriene receptor 1, which regulates TH2 cytokine production. *J. Allergy Clin. Immunol.* **132**: 205–213. CrossRef Google Scholar

55. Pelly, V. S., Y. Kannan, S. M. Coomes, L. J. Entwistle, D. Rückerl, B. Seddon, A. S. MacDonald, A. McKenzie, M. S. Wilson. 2016. IL-4-producing ILC2s are required for the differentiation of T_H2 cells following Heligmosomoides polygyrus infection. *Mucosal Immunol.* **9**: 1407–1417. CrossRef Google Scholar

56. ↵von Moltke, J., C. E. O'Leary, N. A. Barrett, Y. Kanaoka, K. F. Austen, R. M. Locksley. 2017. Leukotrienes provide an NFAT-dependent signal that synergizes with IL-33 to activate ILC2s. *J. Exp. Med.* **214**: 27–37. Abstract/FREE Full Text Google Scholar

57. ↵Talbot, S., R.-E. E. Abdulnour, P. R. Burkett, S. Lee, S. J. F. Cronin, M. A. Pascal, C. Laedermann, S. L. Foster, J. V. Tran, N. Lai, et al. 2015. Silencing nociceptor neurons reduces allergic airway inflammation. *Neuron* **87**: 341–354. Google Scholar

58. ↵Klose, C. S. N., T. Mahlakõiv, J. B. Moeller, L. C. Rankin, A.-L. Flamar, H. Kabata, L. A. Monticelli, S. Moriyama, G. G. Putzel, N. Rakhilin, et al. 2017. The neuropeptide neuromedin U stimulates innate lymphoid cells and type 2 inflammation. *Nature* **549**: 282–286. CrossRef PubMed Google Scholar

59. Wallrapp, A., S. J. Riesenfeld, P. R. Burkett, R.-E. E. Abdulnour, J. Nyman, D. Dionne, M. Hofree, M. S. Cuoco, C. Rodman, D. Farouq, et al. 2017. The neuropeptide NMU amplifies ILC2-driven allergic lung inflammation. *Nature* **549**: 351–356. CrossRef PubMed Google Scholar

60. ↵Cardoso, V., J. Chesné, H. Ribeiro, B. García-Cassani, T. Carvalho, T. Bouchery, K. Shah, N. L. Barbosa-Morais, N. Harris, H. Veiga-Fernandes. 2017. Neuronal regulation of type 2 innate lymphoid cells via neuromedin U. *Nature* **549**: 277–281. CrossRef PubMed Google Scholar

61. ↵von Moltke, J., R. M. Locksley. 2014. I-L-C-2 it: type 2 immunity and group 2 innate lymphoid cells in homeostasis. *Curr. Opin. Immunol.* **31**: 58–65. CrossRef PubMed Google Scholar

62. ↵Owyang, A. M., C. Zaph, E. H. Wilson, K. J. Guild, T. McClanahan, H. R. P. Miller, D. J. Cua, M. Goldschmidt, C. A. Hunter, R. A. Kastelein, D. Artis. 2006. Interleukin 25 regulates type 2 cytokine-dependent immunity and limits chronic inflammation in the gastrointestinal tract. *J. Exp. Med.* **203**: 843–849. Abstract/FREE Full Text Google Scholar

63. ↵Fallon, P. G., S. J. Ballantyne, N. E. Mangan, J. L. Barlow, A. Dasvarma, D. R. Hewett, A. McIlgorm, H. E. Jolin, A. N. J. McKenzie. 2006. Identification of an interleukin (IL)-25-dependent cell population that provides IL-4, IL-5, and IL-13 at the onset of helminth expulsion. *J. Exp. Med.* **203**: 1105–1116. Abstract/FREE Full Text Google Scholar

64. ↵Kang, Z., S. Swaidani, W. Yin, C. Wang, J. L. Barlow, M. F. Gulen, K. Bulek, J. S. Do, M. Aronica, A. N. J. McKenzie, et al. 2012. Epithelial cell-specific Act1 adaptor mediates interleukin-25-dependent helminth expulsion through expansion of Lin(-)c-Kit(+) innate cell population. *Immunity* **36**: 821–833. CrossRef PubMed Google Scholar

65. ↵Urban, J. F. Jr.., N. Noben-Trauth, D. D. Donaldson, K. B. Madden, S. C. Morris, M. Collins, F. D. Finkelman. 1998. IL-13, IL-4Ralpha, and Stat6 are required for the expulsion of the gastrointestinal nematode parasite *Nippostrongylus brasiliensis. Immunity* **8**: 255–264. CrossRef PubMed Google Scholar

66. ↵Bezençon, C., A. Fürholz, F. Raymond, R. Mansourian, S. Métairon, J. Le Coutre, S. Damak. 2008. Murine intesti
expressing Trpm5 are mostly brush cells and express markers of neuronal and inflammatory cells. *J. Comp. Ne*
514–525. CrossRef PubMed Google Scholar

67. ↵Schütz, B., I. Jurastow, S. Bader, C. Ringer, J. von Engelhardt, V. Chubanov, T. Gudermann, M. Diener, W. Kummer, G. Krasteva-Christ, E. Weihe. 2015. Chemical coding and chemosensory properties of cholinergic brush cells in the mouse gastrointestinal and biliary tract. *Front. Physiol.* **6**: 87. CrossRef PubMed Google Scholar

68. ↵Chandrakesan, P., R. May, N. Weygant, D. Qu, W. L. Berry, S. M. Sureban, N. Ali, C. Rao, M. Huycke, M. S. Bronze, C. W. Houchen. 2016. Intestinal tuft cells regulate the ATM mediated DNA Damage response via Dclk1 dependent mechanism for crypt restitution following radiation injury. *Sci. Rep.* **6**: 37667. Google Scholar

69. ↵Höfer, D., B. Püschel, D. Drenckhahn. 1996. Taste receptor-like cells in the rat gut identified by expression of alpha-gustducin. *Proc. Natl. Acad. Sci. USA* **93**: 6631–6634. Abstract/FREE Full Text Google Scholar

70. ↵Bezençon, C., J. le Coutre, S. Damak. 2007. Taste-signaling proteins are coexpressed in solitary intestinal epithelial cells. *Chem. Senses* **32**: 41–49. CrossRef PubMed Google Scholar

71. ↵Kaske, S., G. Krasteva, P. König, W. Kummer, T. Hofmann, T. Gudermann, V. Chubanov. 2007. TRPM5, a taste-signaling transient receptor potential ion-channel, is a ubiquitous signaling component in chemosensory cells. *BMC Neurosci.* **8**: 49. CrossRef PubMed Google Scholar

72. ↵Lu, P., C.-H. Zhang, L. M. Lifshitz, R. ZhuGe. 2017. Extraoral bitter taste receptors in health and disease. *J. Gen. Physiol.* **149**: 181–197. Abstract/FREE Full Text Google Scholar

73. ↵Lei, W., W. Ren, M. Ohmoto, J. F. Urban Jr.., I. Matsumoto, R. F. Margolskee, P. Jiang. 2018. Activation of intestinal tuft cell-expressed Sucnr1 triggers type 2 immunity in the mouse small intestine. *Proc. Natl. Acad. Sci. USA* **115**: 5552–5557. Abstract/FREE Full Text Google Scholar

74. ↵Müller, M., M. Mentel, J. J. van Hellemond, K. Henze, C. Woehle, S. B. Gould, R.-Y. Yu, M. van der Giezen, A. G. M. Tielens, W. F. Martin. 2012. Biochemistry and evolution of anaerobic energy metabolism in eukaryotes. *Microbiol. Mol. Biol. Rev.* **76**: 444–495. Abstract/FREE Full Text Google Scholar

75. ↵Teunis, P. F. M., F. H. A. Sukhrie, H. Vennema, J. Bogerman, M. F. C. Beersma, M. P. G. Koopmans. 2015. Shedding of norovirus in symptomatic and asymptomatic infections. *Epidemiol. Infect.* **143**: 1710–1717. CrossRef Google Scholar

76. ↵Lee, S., C. B. Wilen, A. Orvedahl, B. T. McCune, K.-W. Kim, R. C. Orchard, S. T. Peterson, T. J. Nice, M. T. Baldridge, H. W. Virgin. 2017. Norovirus cell tropism is determined by combinatorial action of a viral non-structural protein and host cytokine. *Cell Host Microbe* **22**: 449–459.e4. CrossRef PubMed Google Scholar

77. ↵Plasschaert, L. W., R. Žilionis, R. Choo-Wing, V. Savova, J. Knehr, G. Roma, A. M. Klein, A. B. Jaffe. 2018. A single-cell atlas of the airway epithelium reveals the CFTR-rich pulmonary ionocyte. *Nature* **560**: 377–381. CrossRef Google Scholar

78. ↵Barham, H. P., S. E. Cooper, C. B. Anderson, M. Tizzano, T. T. Kingdom, T. E. Finger, S. C. Kinnamon, V. R. Ramakrishnan. 2013. Solitary chemosensory cells and bitter taste receptor signaling in human sinonasal mucosa. *Int. Forum Allergy Rhinol.* **3**: 450–457. CrossRef PubMed Google Scholar

79. ↵Tizzano, M., B. D. Gulbransen, A. Vandenbeuch, T. R. Clapp, J. P. Herman, H. M. Sibhatu, M. E. A. Churchill, W. L. Silver, S. C. Kinnamon, T. E. Finger. 2010. Nasal chemosensory cells use bitter taste signaling to detect irritants and bacterial signals. *Proc. Natl. Acad. Sci. USA* **107**: 3210–3215. Abstract/FREE Full Text Google Scholar

80. ↵Lin, W., T. Ogura, R. F. Margolskee, T. E. Finger, D. Restrepo. 2008. TRPM5-expressing solitary chemosensory c respond to odorous irritants. *J. Neurophysiol.* **99**: 1451–1460. CrossRef PubMed Google Scholar

81. ↵Lee, R. J., G. Xiong, J. M. Kofonow, B. Chen, A. Lysenko, P. Jiang, V. Abraham, L. Doghramji, N. D. Adappa, J. N. Palmer, et al. 2012. T2R38 taste receptor polymorphisms underlie susceptibility to upper respiratory infection. *J. Clin. Invest.* **122**: 4145–4159. CrossRef PubMed Google Scholar

82. ↵Krasteva, G., B. J. Canning, P. Hartmann, T. Z. Veres, T. Papadakis, C. Mühlfeld, K. Schliecker, Y. N. Tallini, A. Braun, H. Hackstein, et al. 2011. Cholinergic chemosensory cells in the trachea regulate breathing. *Proc. Natl. Acad. Sci. USA* **108**: 9478–9483. Abstract/FREE Full Text Google Scholar

83. ↵Saunders, C. J., M. Christensen, T. E. Finger, M. Tizzano. 2014. Cholinergic neurotransmission links solitary chemosensory cells to nasal inflammation. *Proc. Natl. Acad. Sci. USA* **111**: 6075–6080. Abstract/FREE Full Text Google Scholar

84. Sharma, P., R. Yi, A. P. Nayak, N. Wang, F. Tang, M. J. Knight, S. Pan, B. Oliver, D. A. Deshpande. 2017. Bitter taste receptor agonists mitigate features of allergic asthma in mice. *Sci. Rep.* **7**: 46166. CrossRef PubMed Google Scholar

85. Sbarbati, A., M. Tizzano, F. Merigo, D. Benati, E. Nicolato, F. Boschi, M. P. Cecchini, I. Scambi, F. Osculati. 2009. Acyl homoserine lactones induce early response in the airway. *Anat. Rec. (Hoboken)* **292**: 439–448. CrossRef PubMed Google Scholar

86. Smith, R. S., S. G. Harris, R. Phipps, B. Iglewski. 2002. The *Pseudomonas aeruginosa* quorum-sensing molecule N-(3-oxododecanoyl)homoserine lactone contributes to virulence and induces inflammation in vivo. *J. Bacteriol.* **184**: 1132–1139. Abstract/FREE Full Text Google Scholar

87. Lee, R. J., J. M. Kofonow, P. L. Rosen, A. P. Siebert, B. Chen, L. Doghramji, G. Xiong, N. D. Adappa, J. N. Palmer, D. W. Kennedy, et al. 2014. Bitter and sweet taste receptors regulate human upper respiratory innate immunity. *J. Clin. Invest.* **124**: 1393–1405. CrossRef PubMed Google Scholar

88. Lee, R. J., B. M. Hariri, D. B. McMahon, B. Chen, L. Doghramji, N. D. Adappa, J. N. Palmer, D. W. Kennedy, P. Jiang, R. F. Margolskee, N. A. Cohen. 2017. Bacterial d-amino acids suppress sinonasal innate immunity through sweet taste receptors in solitary chemosensory cells. *Sci. Signal.* **10**: eaam7703. Abstract/FREE Full Text Google Scholar

89. Barth, A. L., T. L. Pitt. 1996. The high amino-acid content of sputum from cystic fibrosis patients promotes growth of auxotrophic *Pseudomonas aeruginosa*. *J. Med. Microbiol.* **45**: 110–119. CrossRef PubMed Google Scholar

90. Fort, M. M., J. Cheung, D. Yen, J. Li, S. M. Zurawski, S. Lo, S. Menon, T. Clifford, B. Hunte, R. Lesley, et al. 2001. IL-25 induces IL-4, IL-5, and IL-13 and Th2-associated pathologies in vivo. *Immunity* **15**: 985–995. CrossRef PubMed Google Scholar

91. Barlow, J. L., A. Bellosi, C. S. Hardman, L. F. Drynan, S. H. Wong, J. P. Cruickshank, A. N. J. McKenzie. 2012. Innate IL-13-producing nuocytes arise during allergic lung inflammation and contribute to airways hyperreactivity. *J. Allergy Clin. Immunol.* **129**: 191–198.e1–4. CrossRef PubMed Google Scholar

92. Reynolds, J. M., Y.-H. Lee, Y. Shi, X. Wang, P. Angkasekwinai, K. C. Nallaparaju, S. Flaherty, S. H. Chang, H. Watarai, C. Dong. 2015. Interleukin-17B antagonizes interleukin-25-mediated mucosal inflammation. *Immunity* **42**: 692–703. Google Scholar

93. Huang, Y., K. Mao, X. Chen, M.-A. Sun, T. Kawabe, W. Li, N. Usher, J. Zhu, J. F. Urban Jr.., W. E. Paul, R. N. Germa
S1P-dependent interorgan trafficking of group 2 innate lymphoid cells supports host defense. *Science* **359**: 114
Abstract/FREE Full Text Google Scholar

94. Kohanski, M. A., A. D. Workman, N. N. Patel, L.-Y. Hung, J. P. Shtraks, B. Chen, M. Blasetti, L. Doghramji, D. W. Kennedy, N. D. Adappa, et al. 2018. Solitary chemosensory cells are a primary epithelial source of interleukin-25 in chronic rhinosinusitis with nasal polyps. *J. Allergy Clin. Immunol.* **142**: 460–469.e7. Google Scholar

95. Patel, N. N., M. A. Kohanski, I. W. Maina, V. Triantafillou, A. D. Workman, C. C. L. Tong, E. C. Kuan, J. V. Bosso, N. D. Adappa, J. N. Palmer, et al. 2018. Solitary chemosensory cells producing interleukin-25 and group-2 innate lymphoid cells are enriched in chronic rhinosinusitis with nasal polyps. *Int. Forum Allergy Rhinol.* **8**: 900–906. Google Scholar

96. Gordon, R. E., M. Kattan. 1984. Absence of cilia and basal bodies with predominance of brush cells in the respiratory mucosa from a patient with immotile cilia syndrome. *Ultrastruct. Pathol.* **6**: 45–49. PubMed Google Scholar

97. Bornstein, C., S. Nevo, A. Giladi, N. Kadouri, M. Pouzolles, F. Gerbe, E. David, A. Machado, A. Chuprin, B. Tóth, et al. 2018. Single-cell mapping of the thymic stroma identifies IL-25-producing tuft epithelial cells. *Nature* **559**: 622–626 Google Scholar

98. Miller, C. N., I. Proekt, J. von Moltke, K. L. Wells, A. R. Rajpurkar, H. Wang, K. Rattay, I. S. Khan, T. C. Metzger, J. L. Pollack, et al. 2018. Thymic tuft cells promote an IL-4-enriched medulla and shape thymocyte development. *Nature* **559**: 627–631 Google Scholar

99. Voisin, T., A. Bouvier, I. M. Chiu. 2017. Neuro-immune interactions in allergic diseases: novel targets for therapeutics. *Int. Immunol.* **29**: 247–261. Google Scholar

00. Sato, A. 2007. Tuft cells. *Anat. Sci. Int.* **82**: 187–199. CrossRef PubMed Google Scholar

01. Alimohammadi, H., W. L. Silver. 2000. Evidence for nicotinic acetylcholine receptors on nasal trigeminal nerve endings of the rat. *Chem. Senses* **25**: 61–66. CrossRef PubMed Google Scholar

02. Deckmann, K., K. Filipski, G. Krasteva-Christ, M. Fronius, M. Althaus, A. Rafiq, T. Papadakis, L. Renno, I. Jurastow, L. Wessels, et al. 2014. Bitter triggers acetylcholine release from polymodal urethral chemosensory cells and bladder reflexes. *Proc. Natl. Acad. Sci. USA* **111**: 8287–8292. Abstract/FREE Full Text Google Scholar

03. Gautron, L., J. M. Rutkowski, M. D. Burton, W. Wei, Y. Wan, J. K. Elmquist. 2013. Neuronal and nonneuronal cholinergic structures in the mouse gastrointestinal tract and spleen. *J. Comp. Neurol.* **521**: 3741–3767. CrossRef PubMed Google Scholar

04. Chandrakesan, P., R. May, D. Qu, N. Weygant, V. E. Taylor, J. D. Li, N. Ali, S. M. Sureban, M. Qante, T. C. Wang, et al. 2015. Dclk1+ small intestinal epithelial tuft cells display the hallmarks of quiescence and self-renewal. *Oncotarget* **6**: 30876–30886. Google Scholar

05. Delgiorno, K. E., J. C. Hall, K. K. Takeuchi, F. C. Pan, C. J. Halbrook, M. K. Washington, K. P. Olive, J. R. Spence, B. Sipos, C. V. E. Wright, et al. 2014. Identification and manipulation of biliary metaplasia in pancreatic tumors. *Gastroenterology* **146**: 233–244.e5. CrossRef PubMed Google Scholar

06. Hayakawa, Y., K. Sakitani, M. Konishi, S. Asfaha, R. Niikura, H. Tomita, B. W. Renz, Y. Tailor, M. Macchini, M. Middelhoff, et al. 2017. Nerve growth factor promotes gastric tumorigenesis through aberrant cholinergic signaling. *Cancer Cell* **31**: 21–34. CrossRef PubMed Google Scholar

07. Westphalen, C. B., Y. Takemoto, T. Tanaka, M. Macchini, Z. Jiang, B. W. Renz, X. Chen, S. Ormanns, K. Nagar, Y. al. 2016. Dclk1 defines quiescent pancreatic progenitors that promote injury-induced regeneration and tumorigenesis. *Cell Stem Cell* **18**: 441–455. CrossRef PubMed Google Scholar

Michael R. Howitt et al., ImmunoHorizons, 2020

Epithelial STAT6 O-GlcNAcylation drives type 2 mucosal immunity against helminth infection
Ming Zhao et al., J Immunol, 2020

Paneth Cell Specific Lysozyme Regulates Intestinal Mucosal Immune Response by Shaping Gut Microbiota Landscape
Shiyan Yu et al., J Immunol, 2017

Low Thymic Activity and Dendritic Cell Numbers Are Associated with the Immune Response to Primary Viral Infection in Elderly Humans.
Axel Ronald Schulz et al., J Immunol, 2015

Infection by the parasitic helminth Trichinella spiralis activates a Tas2r-mediated signaling pathway in intestinal tuft cells
Xiao-Cui Luo et al., Proc Natl Acad Sci U S A, 2019

Dclk1-expressing tuft cells: critical modulators of the intestinal niche?
Moritz Middelhoff et al., American Journal of Physiology - Gastrointestinal and Liver Physiology, 2017

Taste for danger
Mitch Leslie, Science, 2019

Previous Next

Back to top

In this issue

The Journal of Immunology
Vol. 202, Issue 5
1 Mar 2019

Print
Download PDF
Article Alerts
Email Article
Citation Tools

Share
Tweet
Like 0

Related Articles

No related articles found.