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Immunoepithelial Crosstalk in Regeneration: The Emerging Role of Tuft Cells: A Review

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ABSTRACT

Tuft cells are specialized epithelial cells scattered throughout various mucosal tissues, including the intestine, respiratory tract, and pancreas. Once thought to be rare and functionally inert, tuft cells are now recognized as key chemosensory and immunomodulatory cells with significant roles in maintaining epithelial integrity. Recent studies have revealed their dynamic involvement in tissue regeneration, particularly through interactions with immune cells and local stem cell niches. This review summarizes the current understanding of tuft cell biology and highlights their emerging role in tissue repair across different organ systems. We discuss the signaling pathways, molecular markers, and regenerative potential of tuft cells, as well as their relevance in disease and regenerative medicine.

KEYWORDS: *Tuft cells, Chemosensory epithelial cells, Tissue regeneration, Stem cell niche, Immune modulation, Regenerative medicine.*

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1. INTRODUCTION

A crucial process for preserving and restoring epithelial barriers after trauma or infection is tissue regeneration. The regulation of cell turnover and differentiation depends critically on the coordination between resident stem cells, immune cells, and signaling networks. Tuft cells have been highlighted as key participants in this regenerative process by recent studies [1]. Tuft cells, which are chemosensory epithelial cells, are found in most endoderm-derived organs of mammals [2]. Early microscopy in the intestine and gallbladder noted their presence. Their distinctive tuft of tightly packed blunt microvilli, which led to their identification as tuft cells in gastrointestinal tissues [3]. This prototypical structure is also referred to by the original names for tuft cells in other tissues, such as microvillus cells and brush cells. These cells have been shown by contemporary instruments to have similar gene expression across a variety of tissues. As a result, the consensus in the field is that all transient receptor potential cation channel subfamily M member 5 (TRPM5)+, interleukin (IL)-25+, and POU domain, Regardless of their tissue origin or if they are tuft-like cells, epithelial cells in class 2 are transcription factor 3 (POU2F3)-dependent and express genes involved in eicosanoid production and taste signaling. Tuft cells commonly, but not always or exclusively, express a variety of other proteins, such as choline acetyltransferase (CHAT), doublecortin-like kinase-1 (DCLK1), and advillin [4,5]. There are morphological variations [4,5]. First discovered in the 1950s due to their distinctive form, tuft cells are now understood to be a wide variety of chemosensory cells [3]. Tuft cells, which have historically been a mystery, have been the subject of more research in recent years due to their function in triggering type 2 immune responses and affecting the activity of surrounding epithelial and stromal cells. Their capacity to detect environmental signals and transmit messages through cytokines and neuroactive chemicals enables them to act as regulators and sentinels of tissue regeneration [6]. In the past ten years, there have been significant advancements in the identification, characterization, and functional analysis of tuft cells in a variety of tissues, including: more knowledge about the physiological functions of tuft cells in humans. In particular, tuft cells have been shown to play a role in inflammation, injury, metaplasia, and tumorigenesis—all of which are aspects of both health and disease. The goal of this review Is to bring together what we currently know about the regenerative functions of tuft cells, paying attention to their tissue-specific roles and the underlying molecular processes. Impact on epithelial healing and regeneration.

2. Tuft Cell Biology

2.1. Morphology and Identification

Tuft cells were first identified in the 1950s based on their distinct morphology characterized by a prominent apical tuft of microvilli extending into the lumen [7]. These cells are dispersed within the epithelium of various endoderm-derived organs, including the intestine, gallbladder, and respiratory tract. Tuft cells are further defined by their ultrastructure, which includes an actin-rich rootlet anchoring the microvilli, numerous secretory vesicles, free ribosomes, and tubulovesicular systems that reflect high metabolic activity. Modern studies have shown that tuft cells can be identified by the expression of markers such as DCLK1, TRPM5, POU2F3, CHAT, and advillin, although these are not exclusive [8,9]. Morphological features combined with transcriptional profiling have positioned tuft cells as a distinct epithelial lineage.

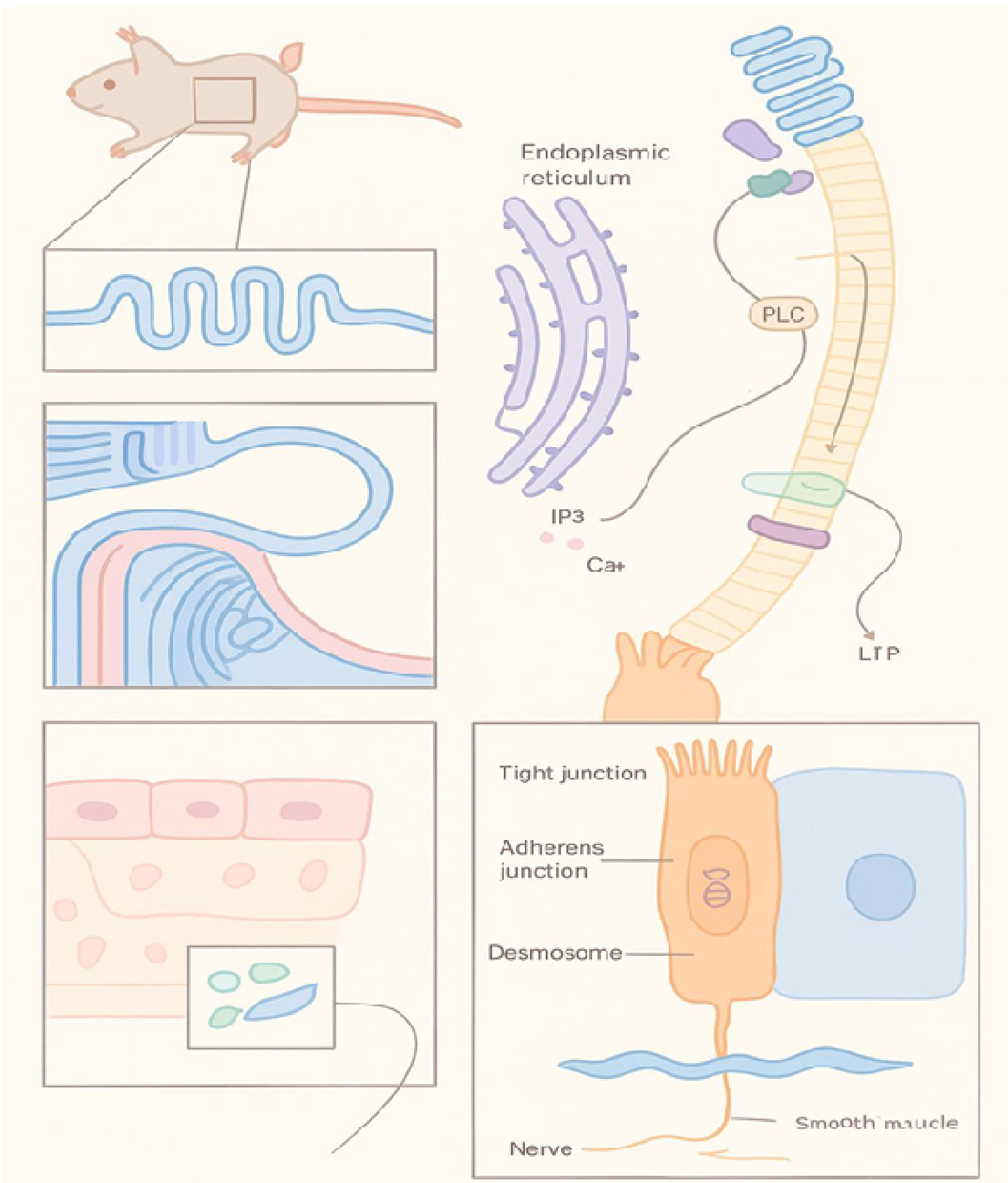

Figure 1. Localization, morphology, and signaling mechanisms of tuft cells in the intestinal epithelium."

2.2. Developmental Origin

Tuft cells originate from the common pool of epithelial progenitor or stem cells that generate the diverse cell types of mucosal epithelia. Like other specialized epithelial lineages, their differentiation follows a tightly regulated program of transcriptional and environmental cues, ensuring appropriate numbers and functional diversity across tissues. Lineage tracing and transcriptomic studies have demonstrated that tuft cells originate from epithelial progenitors and share developmental programs with other mucosal epithelial lineages. Transcription factors play a key role in their differentiation: ATOH1 is required for the early specification of secretory lineages including tuft cells, while POU2F3 acts as the master regulator of tuft cell fate [10]. Additional regulators such as SOX4 and GFI1B refine tuft cell identity and ensure their proper differentiation in a tissue-specific manner [11,12]. Importantly, intestinal tuft cells are relatively rare under homeostatic conditions but can persist long-term, with a subset acting as potential cancer-initiating cells under pathological states [11]. Genetic lineage tracing has also confirmed that tuft cells arise from $Lgr5^+$ intestinal stem cells, and under inflammatory conditions—particularly during type 2 immune activation—they expand in number through IL-25–IL-13–dependent feedback loops [13].

2.3. Functional Characteristics

Despite being a rare epithelial population, tuft cells exert broad influence on mucosal immunity and tissue regeneration. Their chemosensory capacity is mediated by canonical taste transduction pathways, including TRPM5 and GNAT3, which allow them to sense environmental cues and microbial metabolites. One striking example is the detection of succinate, a microbiota-derived metabolite that activates tuft cells via the receptor SUCNR1, triggering IL-25 release and downstream type 2 immune activation [14].

Tuft cells are the dominant epithelial source of IL-25, which activates group 2 innate lymphoid cells (ILC2s). These ILC2s secrete IL-13, which feeds back onto epithelial progenitors to promote tuft and goblet cell hyperplasia, forming the well-characterized "tuft cell–ILC2 circuit" [13].

In addition to immune regulation, tuft cells participate in neuroimmune communication by secreting acetylcholine (ACh) and lipid mediators such as leukotrienes and prostaglandins, which act on nerves, smooth muscle, and immune cells. This places tuft cells at the crossroads of epithelial, neural, and immune interactions [15].Collectively, tuft cells integrate chemosensory detection, immune signaling, and niche regulation, thereby functioning as sentinels and coordinators of epithelial defense and regeneration [7–15].

3. Tuft Cells in the Intestinal Epithelium

The intestinal epithelium is a dynamic and self-renewing barrier, renewed approximately every 3–5 days. Tuft cells, though rare, are strategically positioned within the intestinal crypts and villi, where they sense environmental changes and contribute to mucosal immunity and epithelial regeneration.

3.1. Role in Homeostasis

Under normal physiological conditions, tuft cells represent less than 1% of the intestinal epithelium. They are long-lived and post-mitotic, with low turnover compared to other epithelial lineages. While their precise role in homeostasis remains under investigation, emerging evidence suggests they contribute to baseline immune surveillance by detecting microbial metabolites such as succinate via SUCNR1, maintaining low-level IL-25 production to prime local immune cells, and interacting with enteric neurons to support barrier function [16,18]. Studies using TRPM5 and DCLK1 markers have shown that tuft cell abundance is modulated by the gut microbiota, suggesting a role in microbial-epithelial communication [19,20].

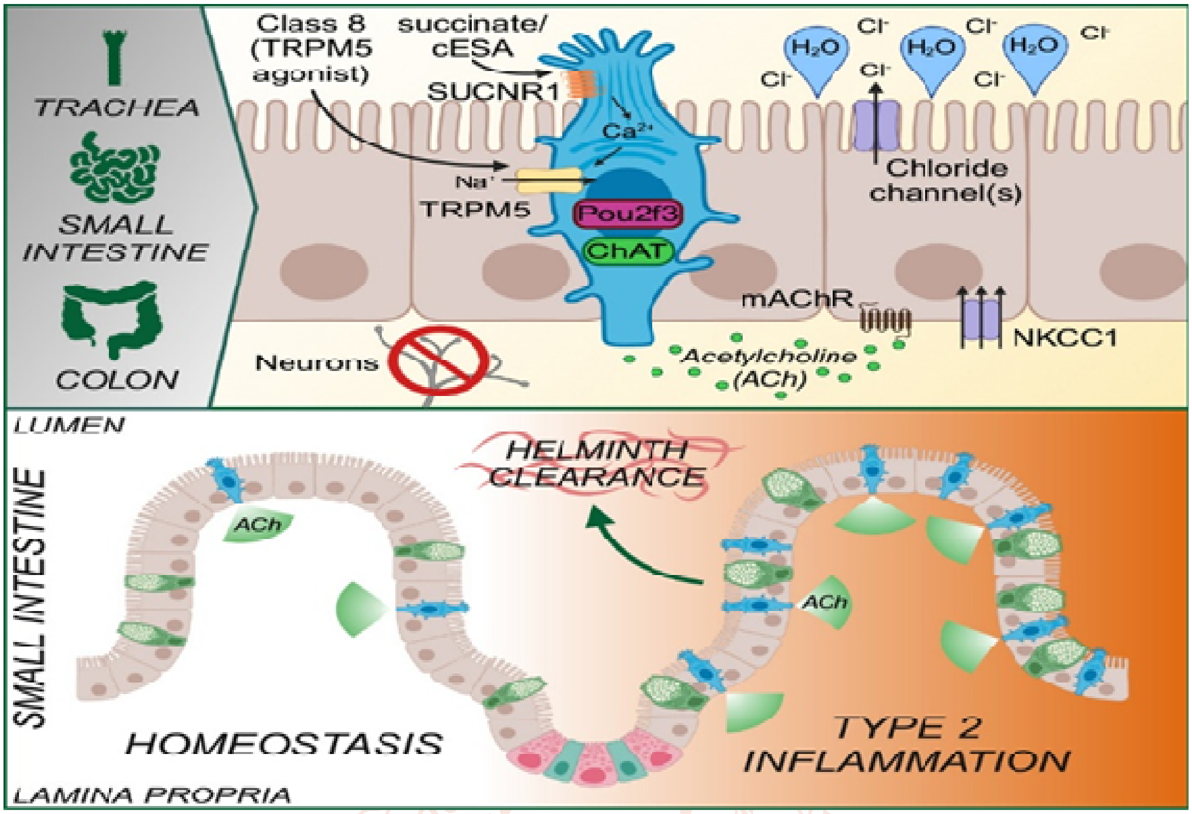

Figure2. 1.Top panel: Tuft cell–mediated acetylcholine release drives chloride and fluid secretion in the airway and gut.
2. Bottom left: Tuft cell signaling maintains intestinal homeostasis under steady-state conditions.
3. Bottom right: Tuft cell activation promotes type 2 inflammation and helminth clearance.

3.2. Response to Injury and Infection

Tuft cells undergo dramatic expansion during intestinal injury and parasitic infection. In helminth-infected or protozoa-colonized mice, tuft cells proliferate in response to luminal signals such as succinate, which activates SUCNR1 and downstream TRPM5 signaling, leading to IL-25 secretion [16,17,18]. This cascade recruits and activates group 2 innate lymphoid cells (ILC2s), which in turn produce IL-13. IL-13 promotes goblet cell hyperplasia, smooth muscle contraction, enhanced epithelial turnover, and Lgr5+ stem cell proliferation. Thus, tuft cells act as upstream regulators in a feedback loop that accelerates tissue repair and pathogen expulsion [16,17].

3.3. Tuft Cells and Stem Cell Niches

Recent studies have uncovered a critical role for tuft cells in regulating the intestinal stem cell (ISC) compartment. Specifically, IL-25/ILC2/IL-13 signaling enhances Wnt and Notch pathways within the crypt base, supporting ISC proliferation and differentiation [16,18]. Tuft cell–derived prostaglandins and acetylcholine also influence the epithelial microenvironment and may affect crypt regeneration [19]. Moreover, tuft cells may secrete BMP inhibitors, tipping the balance toward regeneration. Importantly, tuft cell expansion during regeneration occurs without direct proliferation; instead, they arise from differentiation of crypt progenitors, underscoring their regulatory rather than progenitive role [19,20].

Table 1: Intestinal Tuft Cell Functions

Function	Mechanism	Outcome
Chemo sensation	TRPM5, SUCNR1	Detects succinate, bile acids
Immune activation	IL-25 secretion	ILC2 activation, IL-13 loop
Tissue regeneration	IL-13 signaling	Stem Cell activation, repair
Epithelial remodeling	Acetylcholine, prostaglandins	Goblet cell hyperplasia, renewal

4. Tuft Cells in Airway and Other Tissues

Tuft cells are present not only in the gut but also in several other organs where they play tissue-specific roles in injury detection, immune modulation, and regeneration. The respiratory tract, pancreas, gallbladder, and bile ducts have emerged as important extra-intestinal sites where tuft cells contribute to tissue repair mechanisms.

4.1. Regeneration in the Respiratory Tract
In the airway epithelium, tuft cells—also referred to as solitary chemosensory cells (SCCs)—reside in the trachea, bronchi, and nasal passages. Similar to their intestinal counterparts, they express POU2F3, TRPM5, and IL-25, and are capable of detecting irritants and microbial metabolites. Following epithelial injury (e.g., from allergens, viruses, or chemical exposure), tuft cells are among the first responders: They expand in number in a POU2F3-dependent manner. Secrete IL-25 and leukotrienes, which activate ILC2s and recruit eosinophils and macrophages. Initiate type 2 immune responses that support barrier repair and mucus secretion. Moreover, tuft cells influence the basal stem cell pool, which is essential for airway epithelial regeneration. Through Notch signaling modulation, tuft cells may promote the differentiation of basal cells into secretory or ciliated cells, restoring tissue architecture after injury [21,22].

4.2. Pancreas, Gallbladder, and Other Sites
Though absent in the healthy adult pancreas, tuft cells emerge in response to chronic injury, ductal metaplasia, or inflammatory conditions such as:
Chronic pancreatitis
Biliary obstruction
Ductal adenocarcinoma precursors (PanIN lesions)

In these settings, tuft cells: Express DCLK1, IL-25, and COX enzymes (involved in prostaglandin production).Participate in immune regulation and epithelial remodeling. Possibly derive from acinar or ductal trans differentiation, suggesting injury-induced plasticity [23,24]. In the gallbladder and bile ducts, tuft cells may also emerge during biliary atresia or cholestatic injury. Though their exact function remains unclear, their appearance correlates with epithelial proliferation and remodeling [25].Other rare sites where tuft-like cells have been observed include:
Thymic epithelium Bladder and urethral lining
Middle ear and olfactory epithelium

In all cases, tuft cells are believed to act as local sentinels, coupling sensory input to epithelial or immune responses tailored to the specific organ context.

Table 2: Extra-Intestinal Tuft Cells in Regeneration:

Tissue	Triggers for tuft cell activity	Regenerative Role
Airway	Viral injury	Support stem cell repair
Pancreas	Chronic inflammation	Modulate immune environment
Gallbladder	Bile acid exposure	Potential role in ductal regeneration
Other organs	Context dependent	Under investigation

5. Molecular Mechanisms in Regeneration
Tuft cells influence tissue regeneration not only through their strategic localization but also through a complex network of molecular signals. These include cytokine secretion, immune cell activation, and modulation of local stem and progenitor cells. In this section, we focus on the key signaling pathways and molecular interactions through which tuft cells orchestrate epithelial repair.

5.1. Key Signaling Pathways
Tuft cells exert their regenerative influence through several molecular signaling networks, with the IL-25/ILC2/IL-13 axis being the most extensively characterized. When tuft cells sense injury, infection, or parasitic invasion through their chemosensory receptors, they secrete IL-25 [26,27]. This cytokine activates group 2 innate lymphoid cells (ILC2s), which in turn produce IL-13. The effects of IL-13 are multifaceted: it stimulates goblet cell differentiation to reinforce mucosal barriers, enhances epithelial cell turnover to replace damaged cells, and activates $Lgr5^{+}$ intestinal stem cells to repopulate the epithelial niche [26,28]. Together, these processes ensure rapid repair of the mucosal lining following injury or infection.

In addition to this central axis, tuft cells also modulate other pathways critical to regeneration. By influencing Wnt signaling, they help maintain the stem cell pool in the intestinal crypts, while modulation of Notch signaling governs the balance between absorptive and secretory lineages, thereby fine-tuning epithelial fate decisions during repair [29–31].

In extra-intestinal tissues such as the pancreas and lung, tuft cells have also been implicated in Hedgehog signaling. Their presence in Hedgehog-active environments and their ability to communicate with stromal and progenitor cells via paracrine mechanisms suggest they play a role in regulating morphogen gradients during tissue remodeling, although direct mechanistic evidence remains limited [32,33].

IL-25/ILC2/IL-13 Axis

One of the most well-characterized regenerative pathways initiated by tuft cells involves the IL-25–ILC2–IL-13 loop: Tuft cells secrete IL-25 upon sensing parasitic or injury-induced signals. ILC2s (Group 2 innate lymphoid cells) respond by producing IL-13, which Stimulates goblet cell differentiation Enhances epithelial cell turnover Activates Lgr5+ intestinal stem cells This axis is crucial in restoring mucosal barriers following injury or infection[26, 28].

Wnt and Notch Signaling

Tuft cells can indirectly modulate: Wnt signaling, a key driver of stem cell renewal in tissues like the intestine. Notch signaling, which determines epithelial cell fate decisions (secretory vs. absorptive lineage). Tuft cell-induced IL-13 and eicosanoids (e.g., prostaglandin D_2) influence these pathways by altering the crypt niche environment, promoting regenerative responses after epithelial damage[29-31].

Hedgehog Signaling

In the pancreas and lung, tuft cells have been implicated in Hedgehog pathway modulation, possibly through: Paracrine effects on stromal or immune cells Crosstalk with progenitor populations during injury-induced regeneration. Although direct evidence is limited, tuft cell presence in Hedgehog-active environments suggests a role in morphogen regulation during tissue remodeling[32-33].

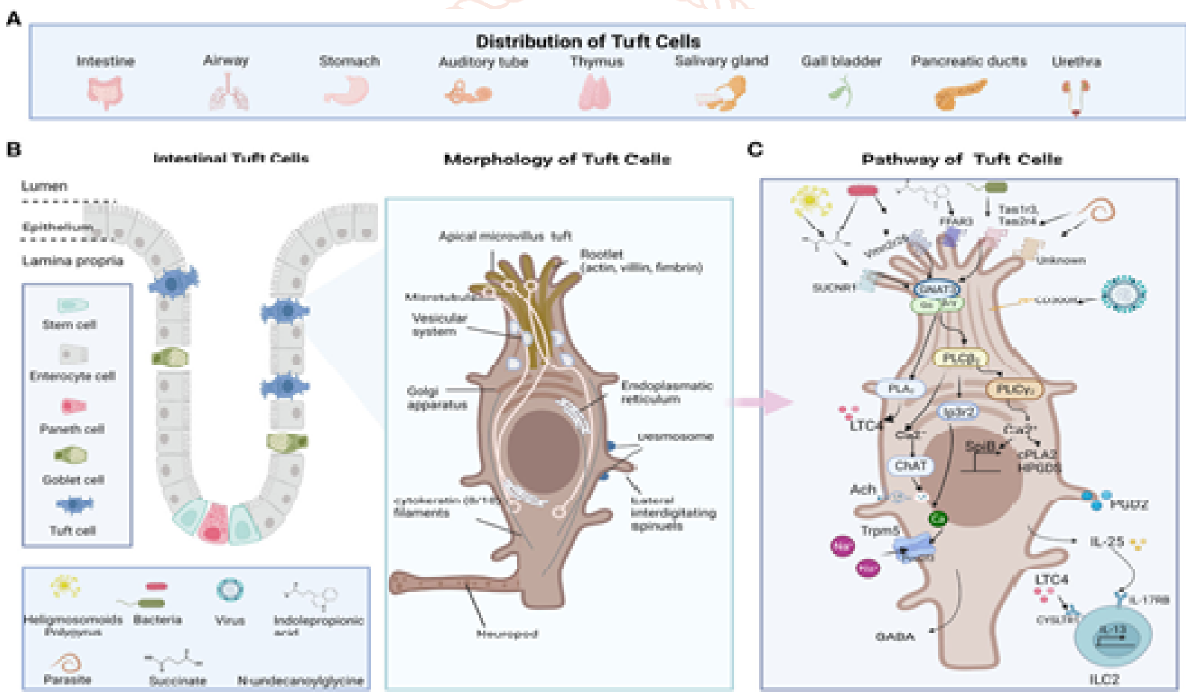

Figure 3. Distribution, morphology, and signaling pathways of tuft cells.

5.2. Tuft Cell–Immune Crosstalk

Beyond direct regenerative signaling, tuft cells function as essential hubs of communication between epithelial and immune compartments. They secrete a range of cytokines, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), which initiate and sustain type 2 immune responses[34].These cytokines recruit and activate immune cells such as eosinophils, mast cells, and ILC2s, which not only defend against pathogens but also release growth-promoting factors that contribute to epithelial repair. Tuft cells additionally produce eicosanoids, such as prostaglandins and leukotrienes, which serve dual roles in modulating inflammation and directing epithelial migration toward sites of damage. [35-37].Another unique feature of tuft cells is their ability to produce acetylcholine, a neurotransmitter that interacts with local neurons and smooth muscle cells. Through this neuro-immune interface, tuft cells influence mucosal motility, barrier tone, and immune cell recruitment, indirectly supporting tissue regeneration[38-40].This multifaceted signaling highlights tuft cells as central regulators of barrier homeostasis, integrating epithelial, immune, and neural responses to ensure coordinated repair after injury.

Tuft cells serve as a central hub in epithelial-immune communication:

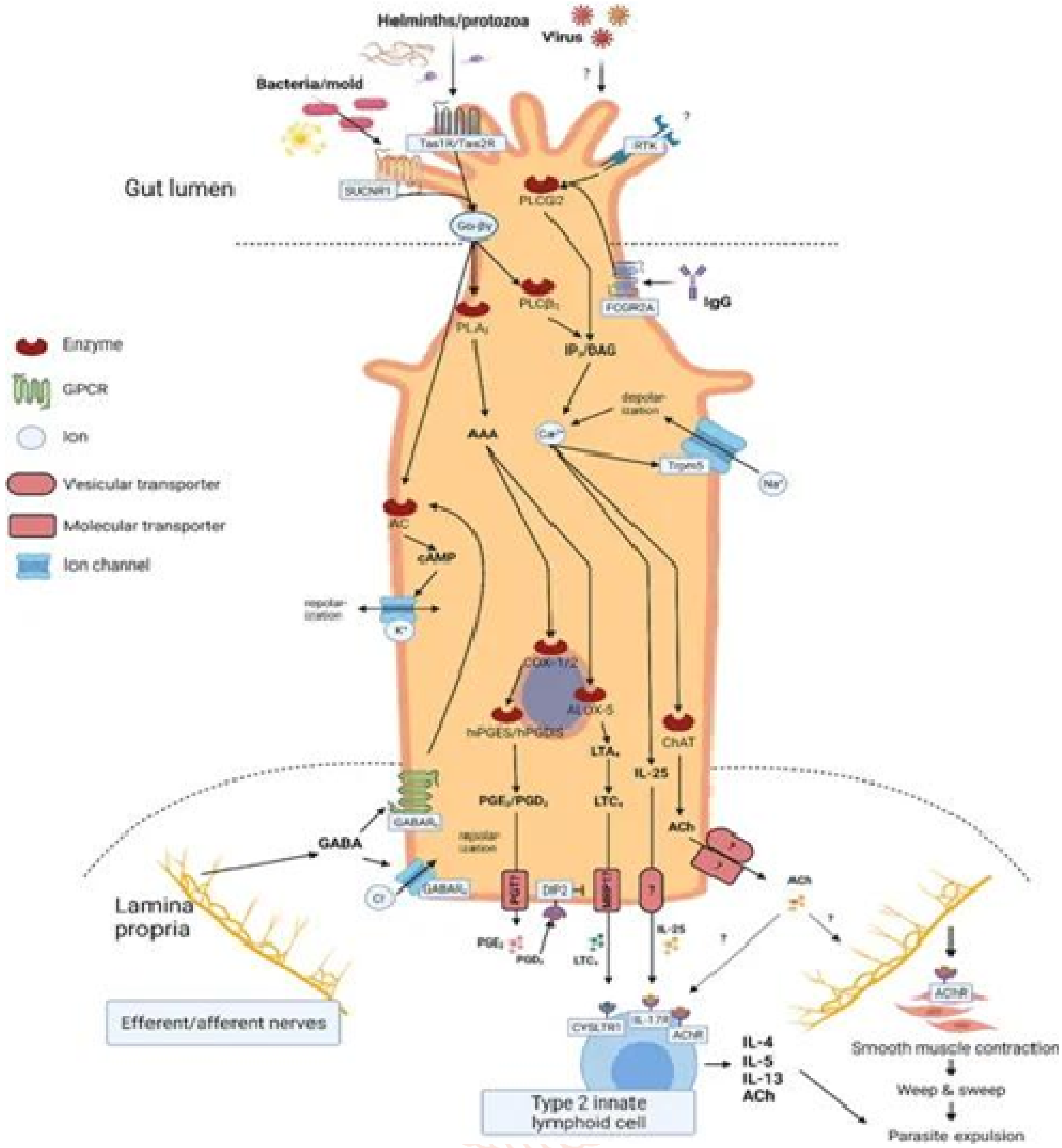

Figure 4 Schematic representation of tuft cell signaling pathways in response to microbial and parasitic stimuli

Cytokine

The release of IL-25, IL-33, and TSLP causes type 2 immunity to activate. IL-25, a crucial cytokine for the initiation of type 2 immunity, is produced by tuft cells (TCs), a key epithelial source. as a component of the immune system The tiny intestine's system promotes type 2 immune responses against helminths, protozoan parasites, and possibly other enteric pathogens [34]. TCs only release minute amounts of IL-25 when in homeostasis, but when they are activated, such as during helminth infection, secretion is significantly increased. The subsequent rapid IL-25-mediated proliferation of ILC2s, which in turn promotes the differentiation of intestinal stem cells, is an early, crucial source of IL-13. cells into a and is crucial to the intestinal "weep and sweep" response, which kills foreign parasites [34,35]. Additionally, IL-4, IL-5, and ACh are released. through ILC2s, which decide the fate of tuft and goblet cells, all of which contribute to the elimination of parasites [36]. The IL-25 anti-helminth response involves other immune cells of the lamina propria in addition to natural killer T cells and nuocytes. In contrast to TCs, which have been demonstrated to be necessary for initiating an adequate anti-helminth reaction [37], their function in the circuit is still unknown.

Eicosanoids

The movement of epithelial cells as well as inflammation are regulated by prostaglandins and leukotrienes. By expressing 5-lipoxygenase, COX-1, and -2, TCs can produce prostaglandin D_2 (PGD_2), prostaglandin E_2 (PGE_2), and cysteinyl leukotriene C_4 (LTC_4) [38]. In addition to their essential physiological functions in homeostasis (e.g., GI motility, secretion, and mucosal protection), these molecules also play a key role in pathological illnesses like inflammatory bowel disease. colorectal cancer and inflammatory bowel illness (IBD) [39]. Although PGE_2 can have either pro- or anti-inflammatory effects depending on the, intestinal inflammation has been linked to elevated COX-2 enzyme activity and PGE_2 synthesis. [39] When induced by helminths or protozoa, the lipoxygenase pathway produces LTC4, which works in synergy with IL-25 but is not necessary for anti-helminth immunity, in contrast to IL-25. which is necessary for getting rid of worms [40]. It's interesting to note that the production and breakdown of LTC4 occur more quickly than that of IL-25 [40].

Neurotransmitters (Acetylcholine)

Tuft cells release acetylcholine (ACh), which indirectly promotes tissue remodeling by influencing neuronal signaling and smooth muscle activity. In addition to being the primary neurotransmitter in cholinergic neurons, ACh also plays a significant role in regulating epithelial proliferation and intestinal function [38]. The only epithelial cell type in the human GI tract that expresses the enzyme choline acetyltransferase (ChAT), which is necessary for the synthesis of ACh, is the TC [39]. It is believed that activation of the canonical taste receptor signaling route is involved in ACh production in TCs, even though the precise stimuli are yet unknown [40]. Recent research indicates that bacterial debris products may activate ACh-dependent auto- and paracrine pathways in chemosensory cells, which would improve mucociliary clearance. It is believed that similar processes apply to how tuft cells operate in the gut [40]. Of the 18 tracheal chemosensory cell subtypes, several might be dismissed as participating in the remaining Ach-signaling. Therefore, more research is necessary, including research on intestinal TCs, before any definitive conclusions can be made about the potential involvement of bitter taste receptors. as well as downstream Ach-induction in general. The vesicular acetylcholine transporter (VAChT), which is found in neurons, is in charge of bringing Ach into secretory organelles for release. However, VAChT is not expressed in murine intestinal TCs except. Although VAChT immunoreactive epithelial cells have previously been identified in the human sigmoid (distal) colon [39], only a few TCs are found in the ascending (proximal) colon. As a result, the release of Ach from TCs is still unknown and might involve distinct secretion mechanisms from those of neurons. For instance, there have been reports of transporters in human sigmoidal epithelium that are capable of exporting Ach from colonic epithelial cells in a non-vesicular manner. many enzymes required for Ach synthesis and choline importers. The possibility of co-localization between these transporters and TCs [40] should be explored in future research. Particularly in barrier tissues like the gut and lung, this crosstalk is crucial for coordinating immune defense and repair processes.

5.3. Tuft Cell Plasticity

Although historically regarded as terminally differentiated chemosensory epithelial cells, emerging evidence suggests that tuft cells may display remarkable plasticity during injury and disease. Under stress or injury conditions, tuft cells have been observed to dedifferentiate or influence lineage reprogramming within the epithelial compartment [41]. This raises the possibility that tuft cells may not only participate passively in repair but also act as active players in regenerative processes. In the pancreas and bile ducts, tuft cells can even appear de novo during metaplastic transformations, suggesting that they may arise from transdifferentiation of other epithelial cell types under injury-induced remodeling [42,43]. Such findings point toward tuft cells being a reactive, regenerative phenotype that emerges to support tissue integrity. Furthermore, tuft cells may serve as a regenerative niche by releasing paracrine signals, cytokines, and growth factors that directly influence basal and stem cell populations, thereby maintaining epithelial integrity under stress. While these roles remain under debate, and lineage-tracing studies are still needed to definitively establish their regenerative capacity, the growing evidence of tuft cell plasticity challenges the long-standing view of them as terminally differentiated and instead positions them as dynamic regulators of tissue regeneration.

6. Clinical Relevance and Therapeutic Potential

Understanding the role of tuft cells in tissue regeneration has opened new avenues for therapeutic strategies in diseases characterized by epithelial damage, chronic inflammation, or defective repair. Their ability to mediate immune responses and interact with stem cell niches positions tuft cells as both biomarkers and potential therapeutic targets in a variety of pathological contexts.

6.1. Tuft Cells in Disease Contexts

Inflammatory Bowel Disease (IBD)

IBD is a collection of persistent idiopathic inflammatory illnesses that cause varying degrees of GI tract inflammation in recurring flares, followed by dormant symptom-free periods [45]. Ulcerative colitis (UC) and Crohn's disease (CD) are the two most prevalent disorders. While both conditions may have symptoms such as stomach pain, the need to have a bowel movement, diarrhea (sometimes bloody), and exhaustion, their pathophysiology differs significantly. Despite the fact that the pathogenesis is still unknown [46], an increasing body of evidence supports the idea that tumor necrosis factor-α (TNF-α), interferon-γ, and other cytokines associated with T helper cell (Th)1 are involved. In the inflamed mucosa of CD patients, IL-12 and Th17-associated cytokines such as IL-17A, IL-21, and IL-23 are significantly elevated, but the cytokine profiles in inflamed mucosal regions in UC patients appear to show increased production of Th2-associated cytokines like IL-4, IL-5, and IL-13 [47]. In contrast, IL-25 has been reported to be significantly reduced in both serum and inflamed intestinal mucosa of patients with flaring IBD when compared to healthy controls [48]. In serum and non-inflamed tissue from individuals with inactive UC and CD, the same pattern was seen. Serum IL-25 levels, however, returned to normal after treatment with infliximab (a TNF-α inhibitor) for IBD flare-ups [49]. In disorders such as UC and CD, tuft cell dysregulation may result in excessive type 2 inflammation or diminished regeneration. An imbalance in the tuft cell–ILC2 signal might upset epithelial homeostasis and worsen mucosal damage. Therapeutic modulation may restore the balance in the inflamed intestine by increasing the quantity of IL-25 or tuft cells [50].

Asthma and Allergic Airway Diseases

Airway tuft cells are increased in asthma models, resulting in type 2 inflammation via leukotrienes and IL-25. Tuft cell–ILC2 activation has been associated with airway remodeling and excessive mucus production. Targeting signals from tuft cells may reduce hyperreactivity and promote a healthy recovery after an injury. Tuft cells play a role in a variety of immune responses throughout the body. After bitter-taste receptors are activated, tuft cells initiate the calcium-dependent production of acetylcholine and orchestrate the release of antimicrobial chemicals by nearby epithelial cells, causing plasma leakage, mast cell degranulation, and neurogenic inflammation [51]. Tuft cells, which are the primary source of interleukin-25, are also a significant producer of cysteinyl leukotrienes, which play a role in the initiation of airway inflammatory processes [52]. Tuft cells have also been shown to arise de novo in the distal airway after a viral infection, implying that they may play a role in dysplastic remodeling and the distal lung's contribution to asthma development [53].

Infections

A critical function for tuft cells in defense against helminths and protozoa has been discovered. Tuft cells react to these parasites by releasing IL-25 and LTC_4, which triggers a chain reaction, leading to eventual elimination of parasitic worms through a type 2 immune response [54]. In general, parasitic worms have immunomodulatory and beneficial effects on the gut. The processes of mucosal healing, inflammation, and function have been thoroughly investigated in both mice and humans [55]. In light of the function of tuft cells in anti-helminthic/protozoan immunity, it is reasonable to consider them as mediators of these effects. Nonetheless, there is very little information available about humans, and helminth therapy does not seem to have any noticeable benefit in comparison to placebo in diseases like IBD [56]. Moreover, helminth therapy has its downsides since extended exposure might result in complications as the host is exposed to a broad variety of helminth-derived products, including potent antigens and inflammatory triggers [57]. Even though short-term administration of Trichuris suis ova (pig worm eggs) seems to be safe and tolerated in humans, prolonged exposure results in immune dysregulation. This dysregulation causes hypo-responsiveness and problems in mounting appropriate immune responses, such as those against neurotropic flaviviruses [58]. The effect is thought to be mediated by tuft cells through an IL-4 signaling pathway, which impairs the CD8+ T cell response [59].

Furthermore, norovirus, the main cause of gastroenteritis worldwide, seems to target tuft cells. In mice, tuft cells express high levels of the murine norovirus receptor CD300lf, which facilitates infection, and they also function as viral reservoirs that cause chronic infections and viral shedding for weeks following the acute phase [60]. Tuft cells aid in the identification and elimination of helminth infections in the intestines and bacterial and viral pathogens in the respiratory system. Tuft cell activation may be used to improve mucosal immunity and hasten epithelial healing following infections [61].

Cancer

Gastric Cancer

Tuft cell markers like DCLK1 have been identified in gastric cancer. Emerging evidence suggests the oncogenic role of tuft cells in gastric cancer. High expression of POU2F3 has been found in neuroendocrine carcinoma of the gastrointestinal tract, including colon, esophageal, and gastric cancers [62]. Inhibition of the tuft cell–ILC2 axis by genetic ablation of tuft cells, ILC2s, or antibody-mediated neutralization of IL-13 or IL-25 reduces gastric tumor development in mice [63]. DCLK1-expressing tuft cells are one of the two main sources of acetylcholine (ACh) within the gastric mucosa. Dual immunofluorescence analysis of cholinergic marker CHAT and tuft cell–specific markers such as advillin has identified tuft cells as the unique source for epithelial biosynthesis of ACh in the human alimentary tract [64]. Notably, ACh secreted by DCLK1+ tuft cells and nerves within the gastric mucosa stimulates nerve growth factor (NGF) expression in gastric epithelium to promote gastric carcinogenesis, while ablation of DCLK1+ cells inhibits epithelial proliferation and tumorigenesis [65]. Thus, this feed-forward ACh–NGF axis derived by tuft cells was suggested as a promising target for the prevention and treatment of gastric carcinoma.

Colon Cancer

Tuft cells are seldom seen in the small intestine under homeostasis, but infection with several related pathogens induces the differentiation of Lgr5 stem cells into tuft cells, which eventually multiply and increase the proportion of goblet cells to aid in pathogen clearance [66]. In the event of tissue damage, intestinal progenitor cells divide rapidly and transform into tuft cells, which help promote type 2 immunity to reduce inflammation and halt the course of ulcerative colitis [67]. Berberine, the primary active ingredient of the herb Coptis chinensis, has been shown to regulate intestinal healing by boosting the IL-25–ILC2–IL-13 immune pathway in tuft cells [68]. Since ulcerative colitis is widely regarded as a precancerous lesion of colon cancer, tuft cells are thought to play a role in its initiation [69].

Lineage tracing studies revealed that DCLK1 labels tumor stem cells that generate tumor progeny in colorectal tumors. Selective ablation of DCLK1-positive tumor stem cells in the intestine results in significant polyp regression without appreciable harm to the normal intestine [70]. DCLK1 depletion has been shown to diminish stemness and prevent tumor growth in the intestines, highlighting its role in controlling tumor cell pluripotency and pro-survival signals [71]. By targeting DCLK1-positive cancer stem cells, tuft cells may offer a unique option for treating colon cancer. In addition, colorectal cancer stem cells have been shown to express IL-17RB, and prolonged depletion of IL-17RB inhibits cancer stem cell development in vivo, confirming IL-17RB+ stem cells as a therapeutic target [72]. Furthermore, in vitro and in vivo studies have demonstrated that SOX9 overexpression plays a role in human colorectal carcinogenesis [73].

6.2. Regenerative Medicine Applications

Therapeutic Activation of Tuft Cell Pathways

Stimulating tuft cell–associated cytokine pathways such as IL-25/ILC2/IL-13 has been proposed to promote epithelial regeneration in damaged tissues, accelerate recovery in chemotherapy-induced mucositis or infectious colitis, and enhance barrier function in vulnerable populations like neonates and the elderly [74–77].

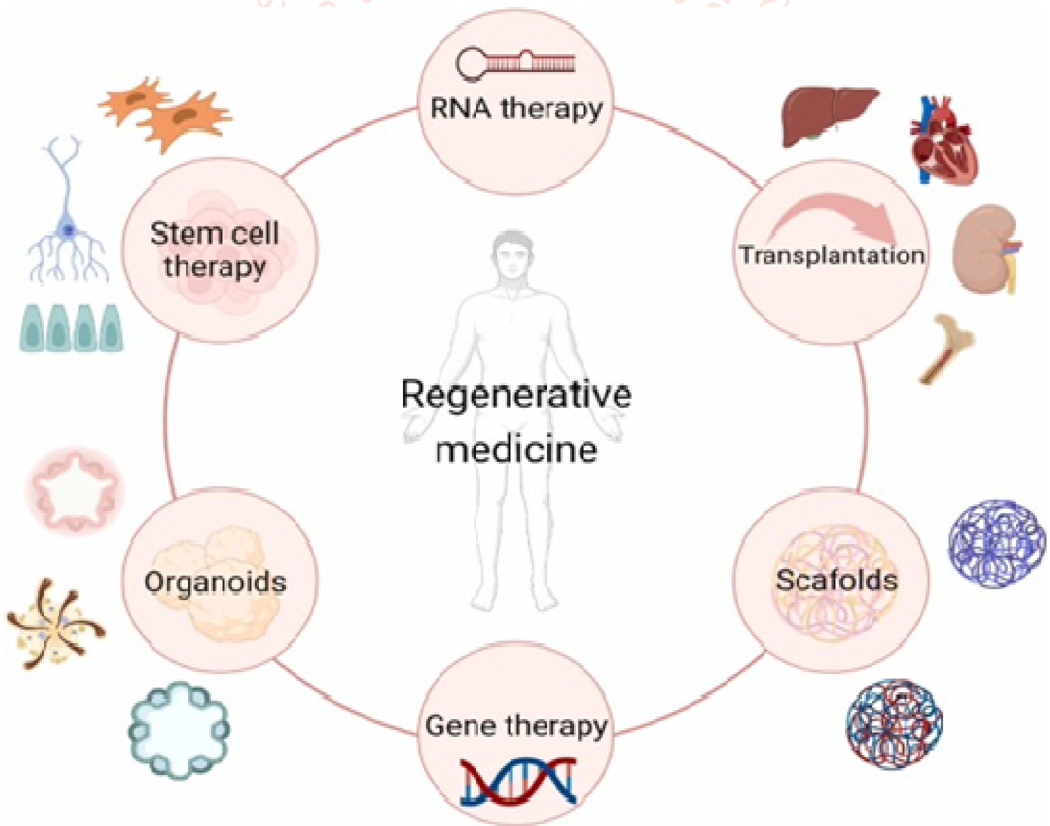

Figure 5,Tuft Cell–Mediated Signaling Pathways and Their Potential Role in Regenerative Medicine

Organoid-Based Models

Tuft cells can be generated in intestinal or airway organoids, which enable drug screening to test tuft-cell-modulating compounds, modeling of infection and regeneration dynamics, and exploration of tuft cell–stem cell interactions in 3D culture [78–80].

Stem Cell Niche Engineering

Modulating the tuft cell niche or mimicking their signals (e.g., IL-25 analogs, prostaglandins) may be useful in bioengineered tissues for transplantation, gut repair therapies in short bowel syndrome or radiation enteritis, and enhancing graft integration in epithelial tissues [81–83].

Table 3:Potential Clinical Strategies Targeting Tuft Cells:

Strategy	Application area
IL-25 modulation	IBD, asthma, epithelial injury
DCLK1 targeted therapies	Cancer stem cells ablation
Tuft cell driven immune activation	Anti-helminth, antiviral responses
Tuft cell signaling mimetics	Tissue engineering, regenerative scaffold

7. Current Challenges and Future Directions

Despite the rapid progress in understanding tuft cell biology, several challenges remain in fully elucidating their role in tissue regeneration. Addressing these knowledge gaps will be crucial for translating basic research into clinical applications.

7.1. Technical Challenges

Tuft cells comprise <1% of epithelial populations, complicating their study with conventional tools [89]. Marker overlap (e.g., DCLK1 in stem cells or cancers) hinders isolation and targeting [84,90]. Lineage tracing models (e.g., POU2F3, TRPM5 reporters) still face limitations in resolution, making it difficult to track tuft cell origin and plasticity [91]. Functional validation is also limited, as ablation often affects broader pathways [92].

7.2. Open Biological Questions

Key questions remain: Can tuft cells dedifferentiate or transdifferentiate into other epithelial types? Do they directly contact stem cells, or act via paracrine signals? What drives organ-specific differences in tuft cell behavior (gut vs. lung vs. pancreas)? How do neuroimmune circuits involving acetylcholine, leukotrienes, and prostaglandins shape regeneration [74,77,93]?

7.3. Future Directions

Advanced Models: Tuft-cell-specific reporter lines (POU2F3-Cre, TRPM5-CreERT2) and organoid/organ-on-chip systems can model epithelial-immune-neural crosstalk [78,91]. Humanized models (patient-derived organoids, xenografts) may bridge gaps between mouse and human biology [80].

Single-Cell & Spatial Multi-Omics: scRNA-seq and ATAC-seq can reveal tuft cell subsets, lineage states, and injury responses, while spatial transcriptomics can map tuft cell proximity to nerves, stem cells, and immune compartments [89,94].

Therapeutic Targeting: IL-25, IL-13, prostaglandins, and receptors such as TRPM5 and SUCNR1 may be druggable targets for tissue repair, infection control, or chronic inflammation [74,82,95]. Tuft cell expansion may aid regenerative medicine (IBD, asthma, pancreatitis), whereas in oncology, tuft-cell-derived signals could act as biomarkers or therapeutic targets [85].

Systems & Translational Directions: Neuroimmune interactions (ACh, leukotrienes, prostaglandins), microbiota metabolites (succinate), and tissue-specific comparisons will guide translation into biomarkers or therapies [77,88,93].

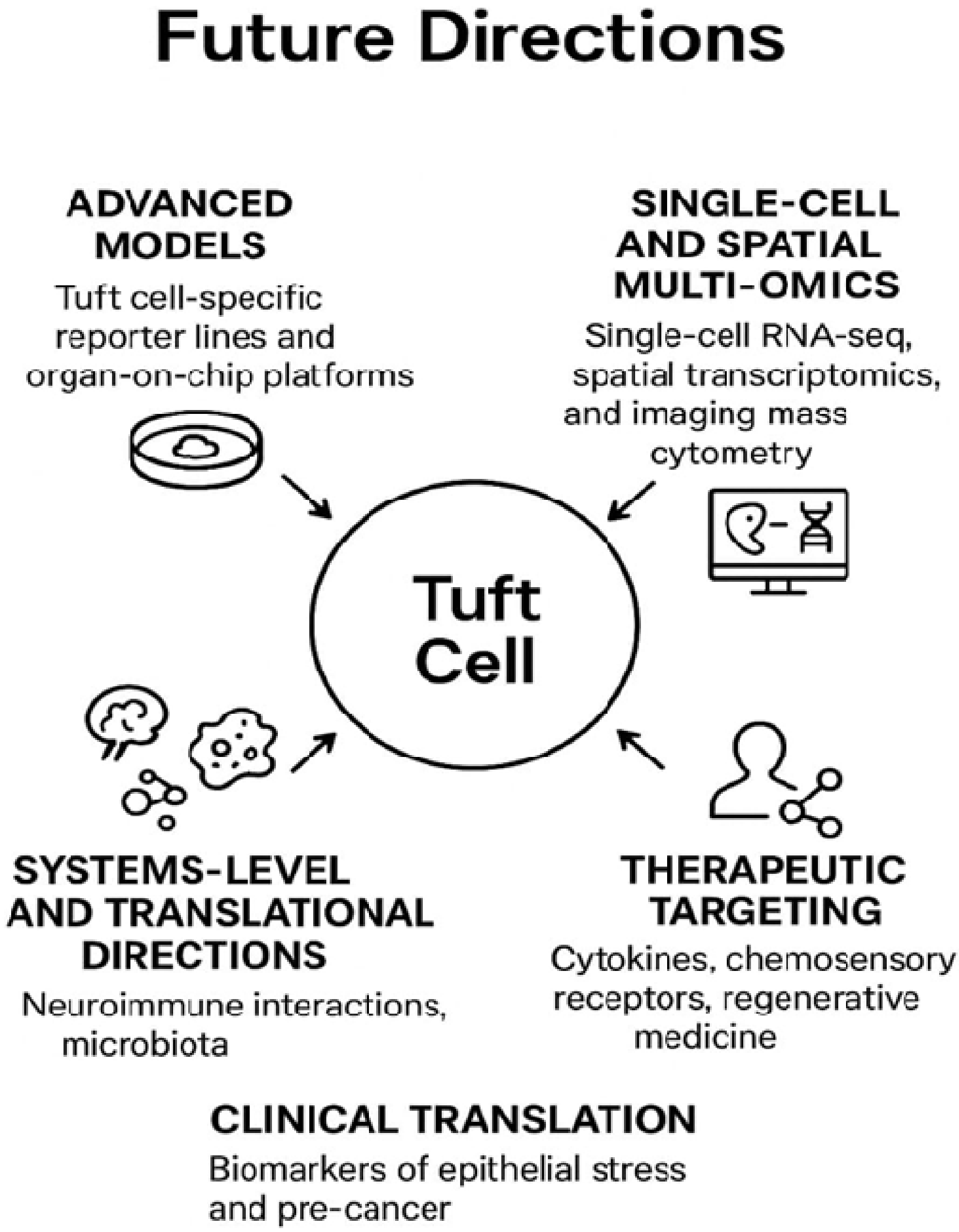

Figure 6 Future Research Directions in Tuft Cell Biology

8. Conclusion

Tuft cells, once enigmatic components of the epithelial landscape, are now emerging as central coordinators of tissue regeneration. Their ability to detect environmental cues, activate immune responses, and modulate the regenerative niche places them at the intersection of sensory, immune, and epithelial biology. While many questions remain about their origin, plasticity, and therapeutic potential, advances in molecular and imaging tools are rapidly expanding our understanding. The integration of emerging technologies, including lineage-specific reporter models, organoid and organ-on-chip systems, and single-cell/spatial multi-omics, promises to address these gaps. Such approaches will not only clarify the heterogeneity of tuft cells across tissues but also reveal how they adapt to injury, infection, and disease. Beyond basic science, the therapeutic implications are profound: tuft cell–derived pathways may represent novel targets for enhancing epithelial repair in inflammatory bowel disease, asthma, pancreatitis, and other barrier-related disorders. At the same time, their involvement in oncogenic transformation highlights the need for careful balance in harnessing tuft cell biology for clinical benefit. Tuft cells may soon shift from a basic research curiosity to a central player in regenerative medicine and epithelial therapy.

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