

ImmunoTools *special* Award 2025



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The progenitors of the tuft cell in the intestine

Tuft cells are specialized epithelial sentinels strategically positioned along the intestinal barrier. They play a critical role in mucosal immune surveillance and the orchestration of type 2 immunity. Upon sensing luminal cues such as helminth parasites or microbial metabolites, tuft cells release a repertoire of effector molecules, including interleukin-25 (IL-25), leukotrienes, acetylcholine, and prostaglandin D₂, which collectively activate type 2 innate lymphoid cells (ILC2s) and coordinate epithelial remodeling.

Tuft cells are derived from Lgr5⁺ intestinal stem cells. Their lineage origin is still debated: Classical models and *in vitro* organoid studies indicate that tuft cells arise from Atoh1⁺ secretory progenitors, similar to goblet and enteroendocrine cells. Conversely, *in vivo* observations using conditional Atoh1 cKO mouse and cytokine-driven differentiation (e.g., IL-13-induced tuft cell expansion) suggest the existence of an Atoh1-independent pathway, pointing to multiple progenitor routes depending on environmental and immunological context. This dual developmental potential implies that tuft cell differentiation is context-dependent, influenced by cytokine milieu and local inflammation. Despite increasing recognition of their importance, the developmental trajectories and molecular heterogeneity of human tuft cells remain largely unexplored.

Scientific Objectives The overarching goal of our project is to elucidate the developmental origin and molecular diversity of intestinal tuft cells under different physiological and pathological conditions. Specifically, we aim to:

1. Identify and characterize the progenitor populations that give rise to tuft cells in intestinal epithelium.
2. Define the transcriptional and signaling signatures distinguishing immunological (IL-25-dominated) and neuro-modulatory (neuropeptide-expressing) tuft cell subsets.
3. Map the relationship between tuft cell heterogeneity and clinical states, such as parasitic infection, inflammatory bowel disease, or epithelial dysregulation.

Experimental Approach Intestinal organoids will be established from biopsy-derived epithelial stem cells. Using optimized differentiation protocols, we will expand tuft cell populations under defined cytokine and growth factor conditions, representing distinct immunological or neuro-active contexts. Single-cell RNA sequencing (scRNA-seq) and high-

resolution immunophenotyping will be performed to delineate tuft cell subpopulations and trace their lineage origin. For accurate identification and functional validation, a panel of anti-human antibodies will be essential, including markers for: Tuft cell identification (e.g., DCLK1, TRPM5, COX1/2, POU2F3), Secretory and progenitor lineage mapping (Atoh1, Lgr5, HES1, MUC2, CHGA), Cytokine and effector molecules (IL-25, IL-13R α 1, TSLP, AREG), Neural signaling components (CHAT, SNAP25, PGP9.5, NMUR1). These antibodies will allow us to validate the identity and state of tuft cells detected by transcriptomics, establish their spatial distribution within organoids and tissue sections, and quantify changes under different experimental stimuli (e.g., IL-13, retinoic acid, helminth antigen).

Expected Outcomes and Impact Through the integration of single-cell sequencing, immunostaining, and functional analysis, this study will generate a comprehensive molecular atlas of intestinal tuft cells and their progenitors. We anticipate revealing: 1. Distinct transcriptional modules linking tuft cell subsets to immune or neuronal functions; 2. The coexistence of Atoh1-dependent and Atoh1-independent tuft lineages; 3. Context-specific tuft cell differentiation pathways driven by cytokines such as IL-13.

Our findings will not only advance the understanding of tuft cell biology and epithelial plasticity but also provide a basis for targeting tuft cell-mediated neuro-immune pathways in intestinal disorders and parasitic infections. Given the essential role of high-quality, well-validated antibodies in defining cell identity and function, the requested antibody panel and cytokines are indispensable for the success of this project.

ImmunoTools *special* AWARD for Xiaogang Feng includes 10 reagents

FITC - conjugated anti-mouse TCR α /b, CD19, CD3, CD45

PE - conjugated anti-mouse CD11b

APC - conjugated anti-human CD4

recombinant human cytokines: IL-13, AREG

recombinant mouse cytokines: IL-13, IL-25

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