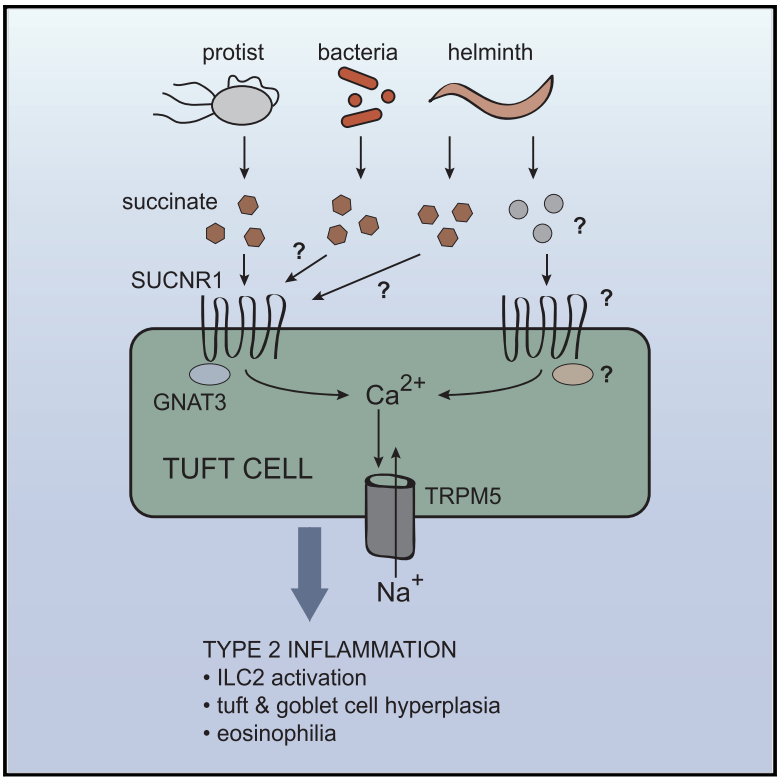
Report

Immunity

Detection of Succinate by Intestinal Tuft Cells Triggers a Type 2 Innate Immune Circuit

Graphical Abstract



Highlights

- Expression of receptors enabling chemosensing on tuft cells is tissue specific
- Tuft cells in the small intestine express the succinate receptor SUCNR1
- Succinate is sufficient to induce a multifaceted type 2 immune response
- Immune sensing of *Tritrichomonas* colonization by tuft cells requires SUCNR1

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In Brief

Tuft cells have been proposed to act as immune sentinels in multiple tissues. Nadjsombati and McGinty et al. now show that detection of the microbial metabolite succinate by tuft cells in the small intestine is sufficient to induce a type 2 immune response, suggesting that tuft cells monitor microbial metabolites to initiate type 2 immunity.

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Detection of Succinate by Intestinal Tuft Cells Triggers a Type 2 Innate Immune Circuit

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SUMMARY

In the small intestine, type 2 responses are regulated by a signaling circuit that involves tuft cells and group 2 innate lymphoid cells (ILC2s). Here, we identified the microbial metabolite succinate as an activating ligand for small intestinal (SI) tuft cells. Sequencing analyses of tuft cells isolated from the small intestine, gall bladder, colon, thymus, and trachea revealed that expression of tuft cell chemosensory receptors is tissue specific. SI tuft cells expressed the succinate receptor (SUCNR1), and providing succinate in drinking water was sufficient to induce a multifaceted type 2 immune response via the tuft-ILC2 circuit. The helminth *Nippostrongylus brasiliensis* and a tritrichomonad protist both secreted succinate as a metabolite. *In vivo* sensing of the tritrichomonad required SUCNR1, whereas *N. brasiliensis* was SUCNR1 independent. These findings define a paradigm wherein tuft cells monitor microbial metabolites to initiate type 2 immunity and suggest the existence of other sensing pathways triggering the response to helminths.

INTRODUCTION

Innate immune sensing, involving the binding of microbially derived ligands to host receptors, is the fundamental first step in the initiation of immune responses to microbes. This ligand-receptor paradigm was first proposed by Charles Janeway (Janeway, 1989) and was soon borne out experimentally by the discovery of toll-like receptor 4, which binds bacterial lipopolysaccharide. In the last two decades, many more innate immune receptors have been discovered, and virtually all of them recognize conserved ligands derived from viruses, bacteria, or fungi. As a result, our understanding of innate immune detection for these classes of pathogens is quite advanced. Much less is known about innate immune sensing of helminths, intestinal protists, and allergens, all of which can induce a type 2 immune response.

Recently, we and others demonstrated that interleukin-25 (IL-25), which is critical for worm clearance (Fallon et al., 2006), is made exclusively by epithelial tuft cells (Gerbe et al., 2016; Howitt et al., 2016; von Moltke et al., 2016). Tuft cells initiate and drive a feed-forward immune signaling circuit that is required for innate and perhaps adaptive type 2 responses in the small intestine. In this circuit, tuft-cell-derived IL-25 induces IL-13 production by group 2 innate lymphoid cells (ILC2s) in the lamina propria. IL-13 then signals in undifferentiated epithelial progenitors, biasing their lineage commitment toward goblet and tuft cells, the latter of which further promote ILC2 activation, resulting in the feed-forward loop that we will refer to as the tuft-ILC2 circuit. Because the entire intestinal epithelium is replaced every 5–7 days (Barker, 2014), the induction of IL-13 leads to rapid epithelial remodeling marked by goblet and tuft cell hyperplasia. Furthermore, production of IL-13, IL-5, and IL-9 by ILC2s promotes eosinophilia and other hallmarks of a type 2 immune response.

In most specific-pathogen-free (SPF) mice, activation of the tuft-ILC2 circuit is restrained and tuft cells, representing <1% of all epithelial cells, are rare (Gerbe et al., 2016). However, flagellated protists of the *Tritrichomonas* genus are found in the intestinal flora of mice in many vivariums (Chudnovskiy et al., 2016; Escalante et al., 2016; Howitt et al., 2016), and at least one species of *Tritrichomonas* is known to activate the tuft-ILC2 circuit (Howitt et al., 2016). In addition, infection with helminths such as the hookworm *Nippostrongylus brasiliensis* leads to even greater activation of the circuit, and in this context tuft cell frequency increases about 10-fold within 7–9 days, corresponding to the time frame in which worms are cleared (von Moltke et al., 2016). However, although several