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Tuft Cells ILC2 Interactions

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Abstract: *Intestinal layer covered by epithelial cells that organized to perform different vital functions starting from nutrients absorption tosense microbes andas a barrier function to induce suitable immuneresponses. Tuft cell and type 2 innate lymphoid cells (ILC2s) are response to helminths and initiate type 2 immune response giving enough ability to expel.*

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I. Introduction

The small intestine like other tissues comprises primary undifferentiated cells. These primary cells are regenerative cells termed as intestinal stem cells (ISCs) arresting in proliferative crypts generating different lineages differentiated to small intestinal cells. These primary cells are considered as a reserve source providing newly synthesized cells instead of previous damaged or old cells. ISC in the crypts comprised of epithelial, subepithelial, and luminal components important in paracrine signals (1). The intestinal epithelium comprised of different types of cells which originated in the crypts and extends into the underline mesenchyme, and upper side protrudes by villi into the lumen. Mostly crypts covered by proliferative cells while villi covered by differentiated cells. The stem cells, which are needed for the rapid compensation of the lost villi cells, are placed in the bottom of the crypts, but their accurate exact nature remains not clear (2).

Innate lymphoid cells (ILCs) are newly discovered in recent years. ILCs are a class of immune cells; whereas ILCs related researches are one of the hot spots and frontiers of immunology. ILCs develop before birth and express receptors according to the surrounding environments, and has similar functions to that of $CD4^{+}$T cells (3). ILCs reside mostly at innate barrier sites such as intestine whereas adaptive lymphocytes are positioned abundantly at lymphoid organs. Consequently, to their location, ILCs are considered as one of the most important immune cells responder for tissue invaders, these results are concluded from many immunological related studies. As other innate immune cells, ILCs, play an intermediate role to stimulate subsequent adaptive immune cells such as naive adaptive lymphocytes by releasing suitable cytokines (4).

Histology of small intestines

Intestinal stem cells ISCs organized either active cycling crypt-based columnar cells (CBCs) or quiescent label-retaining cells (LRCs) located at position 4 of the crypt (5, 6). Lgr5 is found to be a common molecular marker of CBC-class ISCs through seminal studies that persevere, self-renewal, to produce all upper differentiated mature epithelial cells in vivo (7). Other molecular markers identified are Olfm4, Ascl2, Prom1, Sox9lo, Cd24lo, Cd166, Grp78, and Lrig1(8-11).

The intestinal histology comprises from two different kinds of mature lineages are absorptive enterocytes and secretory cells. The most abundant mature intestinal cells are enterocytes; while secretory cells make up a smaller proportion. Secretory cells divided into four different classes: enteroendocrine cells, goblet cells, Paneth cells, and tuft cells (or brush cells) (12). The main function of enteroendocrine cells is hormone secretion in response to macronutrients, goblet cells produce a dynamic barrier of mucus layer, and Paneth cells are responsible for maintenance of stem cell homeostasis and immune-related function which are responsible for

the production of antimicrobial peptides (12). There are additional intestinal cell types: microfold (M) cells, cup cells, and tuft cells. M cells are abundant over the gut-associated lymphoid follicles and connect between the lumen and the underlying immune cells (13). The cup cells comprise about 6% of ileum epithelium, which is characterized by short brush border and distinct particles in their microvillus membrane. The plasma membrane of cup cells undergo glycosylation unlike M cells but lack immune barrier function like loading of luminal pathogenic antigens to the mucosal immune cells (14). The rare seventh intestinal epithelial cell type is tuft cells, and are composed about 0.4 % of total mouse intestinal epithelium. The function of tuft cells was not clear until recently, despite its being discovered almost 50 years ago (15-18).

The other type of intestinal epithelium is the absorptive cells residing into crypts and villi, each three to five days these cells turn over. The capacity of the reserved cells in the crypts to produce newly differentiated cells keep balanced to compensate for the loss of cells in the villi by apoptosis. Functional identification was difficult until now for the intestinal stem cells due to lacking unique markers. Although the steady renewing fashion of the crypt stem cells to produce transit-amplifying cells, the stem cells have enough capability to rise to all further differentiated lineages (19).

Three of well-differentiated villus cells (enterocytes, goblet cells, and enteroendocrine cells) are originated and trend to migrate continuously from crypt-villus junction toward the crypt-villus axis. Different crypts are shared to produce these mature cells into each villus (20).

The fourth intestinal differentiated cell type is the Paneth cell, which locates at the crypt bottom. Lgr5 stem cells are found to distribute between well-differentiated Paneth cells. Paneth cells produce antibacterial peptides like lysozyme and cryptdins/defensins. In the colon, also epithelium layer covers crypts, with a flat surface instead of taking villi. Colon epithelium also divided into two different cell types: the absorptive colonocytes and the goblet cells. In the colon such stem cells have not detected (21). Physically Lgr5 stem and Paneth cells are constantly distributed in the crypts. Paneth cells contain surface markers including EGF, TGF-a, Wnt3, and the Notch ligand Dll4 which are essential for the stem-cell maintenance in culture as essential signals. Removal of these Paneth cell signals resulted in the associated loss of Lgr5 stem cells meaning that Lgr5 stem cells provide their important signals for essential niche signals from its existent formed cells, the Paneth cells (22).

Tuft cells

Intestinal tuft cells are a specific absorptive intestinal epithelial cell. Tuft cells are one of the mucosal epithelial cells, which are characterized by their specialized fusiform character and apical microvilli protruding into the lumen of the intestine (23-25). The tuft cells were discovered some five decades ago in the trachea of rat (26) and in the glandular stomach of the mouse (25). Tuft cells are spread within the mucosal layer of the gastrointestinal (GI) tract, which the number of constituents decline gradually in the jejunum colon direction (27). They have an intracellular tubular network across microvilli and endoplasmic reticulum, facilitating materials exchange to and from the cells (28).

Tuft cells description was difficult because they lack differential unique molecular markers, in addition to unclearly defined function, but now some functional studies have been raised to characterize tuft cells related functions. At the same time, some newly discovered markers allow breeding mouse lines in which they specifically create some reporters of interest in uniquely expressed tuft cells. This development in the tuft cells structure and function turn the understanding of tuft cells into much clear than before(23, 29).

Tuft cells interact with neighbor cells by lateral projections to access into the nuclei of the adjacent cell (28). GI tuft cells play as a chemosensory cell type, connecting between lumen, neurons and endocrine cells (30, 31). A number of tuft cells are detected closely contacted with satiety-associated endocrine cells and express cholecystokinin, peptide YY and glucagon-like peptide1 (27). In addition, tuft cells also found between nerve fibres(32, 33).

The first extension of primary stem cells is to produce more defined progenitors called ‘‘transit-amplifying’’zone. These tuft cells are continuously seeded from amplified stem cells located in the crypts, but this progression stops when these newly formed tuft cells reach the crypt-villus boundary remaining just post-mitotic cells in the villus (5, 7, 34).

The first demonstration of tuft cells was done by Rhodin and Dalhamn, who described in the rat trachea (26), and Ja¨rvi and Keyrilainen who observed in glandular stomach of mice (25). Then tuft cells were later seen in the respiratory system (17, 35-39), and the gastrointestinal tract (18, 40), of various mammals such as human, pig, rat, cat, cow, ferret, guinea pig, rabbit, and mouse. Depend on morphological shape tuft cells were called peculiar’’, ‘‘fibrillovesicular’’, ‘‘caveolated’’, ‘‘brush’’, or ‘‘tuft’’ cells. All of these names depended on the tuft cells unique morphology with its apical bundles of microfilaments and thick microvilli extending into the intestinal lumen. Since 2005 a workgroup, after they raised a recommendation, started to study possible tuft cells function/s according to their location in the gut (41)

Detection of molecular markers allowed scientists to study the tuft cells nature, functions, and origins.

Actin filaments such as villin and fimbrin tubulin network and ankyrin family proteins were detected in tuft cells which suggested the position of tuft cells for different functions from the rest of the cells (17, 42).

The detected molecular markers of tuft cells, despite, their similarity to enterocytes, but they are more suitable to tuft cells located in the respiratory system, and in the epithelia of the gastric and pancreatic duct. Other markers such as cytokeratin 18 (CK-18) filaments, neurofilaments (43, 44), microtubule-linked protein kinase Dclk1 (Dcamkl-1 as well), and actin filaments, acetylated tubulin (ac-tubulin) are greatly limited to tuft cells. Particularly, CK-18, neurofilaments, and Dclk1 have not been detected in other cells (45-47).

The first molecular markers detected in tuft cells are similar to lingual taste bud cells which suggest that tuft cells are one of the chemosensory cells. In addition to taste signal transducer molecules which improved this hypothesis has been detected such as Met-Enkephalin, and TRPM5 (48-51). Other taste related receptors were found shared with other intestinal cells. Enteroendocrine cells shared GLP-1/GIP with tuft cells (52, 53) and T1R1 and T1R3 are found to express in tuft cells as Paneath cells (54, 55). Tuft cells were proposed to be one of gut chemosensory cells with gut enteroendocrine cells (EECs). This hypothesis was supported after discovering of G protein-coupled receptors (GPCRs) on tuft cells and EECs. In addition to that these two cell types linked to sensory nerves in the sub-mucosal area. Nutrient exposing in the gut activates expression of GPCRs on tuft cells, EECs, and submucosal nerves, which control epithelial cell proliferation, physiological gastrointestinal function, and metabolism (31).

Tuft cell development during the embryonic period appears pretty late but the exact time is not known in mammals. Cellular markers expressed in different time points such as Dclk1 expression in mice start to detect in the intestine after 1 week after birth, a-tubulin appears in E16.5 (47) and Gfi1in E18.5 in mice (56). In the rat, tuft cells are detected after birth and in the stomach and more abundantly at the end of sucking period (57). In humans, tuft cells appeared after 5 months of the fetus development in the small intestine (58).

To address the location of tuft cells, Tsubouchi et al, injected mice by 3H-thymidine, then tuft cells were observed in the inferior side of the crypt (59). Excessive mutagenesis studies suggested that enterocytes, tuft cells, and goblet cells collectively differentiated from a common progenitor or stem cell (34). In BrdU studies, tuft cell life was approximately confirmed to a renewed each 1 week at least (46). After genetic tracing studies, (7, 60) tuft cells origin was further confirmed from Lgr5-expressing crypt columnar stem cells like enterocytes, enteroendocrine, Paneth and goblet cells (46). Tuft cells expressing Dclk1 were detected in post-mitotic cells (45), and then tuft cells were considered as one of the long-lived quiescent stem cells (61, 62).

Tuft cells and disease

The probable involvement of tuft cells in specific diseases is not well known. Studies confirming this potential relation are still rare. The respiratory tract tuft cells are involved to replace tracheal ciliated cells in immotile cilia syndrome (63). A different study was conducted in an infant suffers from bilateral pneumothoraces and respiratory distress, and histological sections from lung displayed desquamative interstitial pneumonitis showing abundant alveolar tuft cells (64). The reason for tuft cells hyperplasia is unknown whether it was because of the disease or increased as a result of respiratory distress. Unlike humans, alveolar tuft cells are increased dramatically following bleomycin-induced interstitial pneumonia (65), stomach inflammation, hyperplasia, and metaplasia in mice. In a different way, human tuft cells are found to increase under specific conditions such as in gastric inflammation or in the metaplastic intestine (47).

In cancer, although the association with tuft cell number is fuzzy, in mouse adenoma tuft cell marker such as Dclk1 was detected and observed rarely in human dysplastic lesions or colon carcinoma (47). In addition to that, morphologically similar cells to tuft cells were found in a fibrillo-caveolated carcinoma, given that tuft cells in some may go through transformation (66). Furthermore, $DCLK1^{+}$ tuft cells are considerably amplified in a number of inflammatory induced carcinogenesis models, suggesting a feasible role of tuft cells in cancer transformation (67, 68). Westphalen et al, generated Dclk1-CreERT BAC transgenic mice, in which contains two intact endogenous Dclk1 loci. More essentially, $DCLK1^{+}$cells remain inactive and extended life but become potent colon-cancer-initiating cells (69).

Also, tuft cells were found with a potent role in inducing an effective immune response against some infectious diseases. Tuft cells in the intestinal epithelium are organized to sense the introduction of foreign microorganisms. For instance, tuft cells have CD300lf, which is a murine norovirus (MNoV) receptor. After infection with norovirus, type 2 cytokines released leading to tuft cell proliferation and then induce a tropism for tuft cells to promote norovirus infection (70).

A big turn in tuft cells function was identified later. Jay et al. found that tuft cells have been increased significantly after *Nippostrongylusbrasiliensis* or *Heligmosomoidespolygyrus*infections, which induce IL4/IL13 signaling-pathway. The function of tuft cells in generating type 2 immune response was confirmed after using Pou2f3 knockout mice that deficient in tuft cells other than that the immune response was diminished for a great extent. That was clear in Th2 and ILC2 cells impaired recruitment and poor production of type 2 immune response cytokines IL13, IL25, and IL33. As a result of this inhibition, goblet cell hyperplasia was greatly

abolished and removal of the worm was delayed. Then they investigate the source after different independent studies (30, 71, 72). This commonly identified function of tuft cells is initiating type 2 immune response after helminth infection and also stimulate allergies (73). Activation of type 2 helper T cells (Th2 cells) and group 2 innate lymphoid cells (ILC2s) as a result of epithelial cell-produced cytokines, such as IL25, IL33 and thymic stromal lymphopoietin considered as a sign of type 2 immune responses (74-76). Th2 cells and ILC2s produce IL13 to mediate intestinal epithelium remodeling, which is characterized by an increase for the number of tuft cells, goblet cells, and smooth muscle cells during the time of worm removal (77). Tuft cells after parasite infections were found to be type 2 immune response initiator cell, by the production of IL25 (71).

Similarly, Locksley's group found similar conclusions after they used an incredible mouse model that has both IL25 expressing reporter as well as inducible Il25 gene deletion. Deletion of Il25 gene in parasitic infected mice consequently displayed similar complications as well as tuft cell deficiency, confirming that IL25 is mainly produced by tuft cells, following parasite infections (72). Another study found the chemosensory function of tuft cells during helminth infections. Mice deficient in TRPM5 cation channel, functioned in signals transduction from numerous taste chemosensory G protein-coupled receptors (78), type 2 response during *Tritrichomonas* infection significantly impaired and lowers IL25 expression and IL17RB ILC2s frequency in the lamina propria. This means that TRPM5 is important in the initiation of type 2 immunity, which stimulates with IL25 cytokine (30).

Immune resident lymphocytes (ILCs)

ILCs share some similarities with other immune cells such as mucosal-associated invariant T (MAIT) cells, γδ T cells, intra-epithelial lymphocytes (IELs), and natural killer T (NKT). ILCs are divided into two broad categories: cytotoxic ILCs (NK cells) and helper ILCs. Helper ILCs and helper T cells (Th) are very comparable in character and function and are divided into three subclasses: ILC1 expressing IFN-γ, IL-1 while ILC2, and ILC3 express IL-17 or IL-22. Uniquely, ILCs do not express T cell Receptors (TCRs) or B cell receptors (BCRs), lacking antigen-specific recognition receptors, and are also different from classical innate immune cells, which their activation does not depend on recognition of pathogen-associated molecular patterns (PAMPs) with pattern recognition receptors (PRRs). Their response is independent of antigen recognition, and polarized effector cells arise during their growth rather than antigenic stimulation. Despite these characters is similar to T cell, ILCs has a different physiological function but is similar to natural killer (NK) cells (79). Three ILCs subsets ILC1, ILC2, and ILC3 are divided into adaptive lymphocytes counterparts Th1, Th2, and Th17 (80). In the early stages of infection or tissue damage, epithelial tissue or other cells release "early warning" cytokines, ILCs can directly identify these "early warning" factor, activate itself, and secrete effector cytokines, for the immune defense to build the first Line of defense (81, 82).

ILCs related interesting studies have established various functions, such as initiate host immune response against pathogens and regulate intestinal microbiota sensing. Moreover, ILCs regulate tissue repair and woundhealing, and oppositely they also endorse inflammatory destruction and tumor growth (83, 84). In mouse lacking, ILCs delayed adaptive immune response was observed, but little effect seen in concluding outcomes (85).

ILCs are firstly originated in the fetal liver from lymphoid progenitors and then start to arise from bone marrow. Unique transcription factors regulate ILCs development but not B or T lymphocytes and then also regulate their maturation away from NK cells and lymphoid tissue inducer (LTi) cells. Common lymphoid precursors develop to innate lymphoid precursors (CILPs), and then direct their maturation separately from T and B cells. Common helper-like ILC progenitors (CHILPs) arises later and develop to ILC1s, ILC2s, ILC3s, and LTi cells but not NK cells; and in the end to ILC progenitors (ILCPs) that arise helper-like ILC1s, ILC2s, and ILC3s. In humans ILC development, the progenitor cells CILPs that are responsible for ILC1s, ILC2s, ILC3s, and NK cells generation are less well characterized (86, 87).

ILCs and disease

ILCs are abundant at pathogen invasion sites which confirm ILCs barrier function. Recent studies established the innate role of ILCs in protection against infection with viruses, bacteria, fungi, and parasites. Localization of ILCs at the barrier sites start during embryonic development and later migrate in response to inflammatory mediators. Like other immune cells tuft cells respond to alarming cytokines, ILCs rapidly activate and migrate to the site of infection (79, 88). In response to infection both epithelial cells and myeloid cell lineages coordinately recognize and react against pathogen to generate suitable and sufficient host protection and also recruit other supporting cells by production of target cytokines and alarmins. IL-12, IL-15 and IL-18 stimulate NK cells and ILC1s, whereas IL-2, IL-4, IL-25, IL-33, thymic stromal lymphopoietin (TSLP), IL-9, and TL1A all together induce ILC2s, as well, IL-1β and IL-23 activate ILC3 responses (89-94).

Like NK cells in killing intracellular viruses, ILC1s and ILC3s have been found as innate cells that have a capability for destroying intracellular bacteria and parasites. ILC1s produce INF-γ to revisit against some

intracellular microorganisms such as *salmonella enterica*subsp, and *Toxoplasma gondi*i infection in the intestine (95). ILC3s also found to produce IL22 in their role to clear the intestine from some extracellular Gram-negative bacterium such as *citrobacterrodentium*. ILC1s and ILC3s responses are considered as innate immune response reflecting their rapid response prior adaptive immune cells recruitments and also their position in the barrier sites reflect their innate responses which have also found to produce suitable antimicrobial bacteria. In addition to the production of IL22, ILC3s also produce IFNγ and IL-17 which these cytokines were detected to increase after a bacillus Calmette-Guérin (BCG) vaccination to protect against *Mycobacterium tuberculosis* infection (96). However, ILCs are considered as innate immune cells but they have similar adaptive immune cells characters. ILC1s and ILC3s enhance immune protection against intracellular microbes, ILC2s are important to response to extracellular helminth parasites (97). ILC2s stimulate type 2 immune response through releasing some effector cytokines such as IL-4, IL-5, IL-9, and IL-13. Type 2 immune responses characterized by immune cells activation such as macrophages and granulocyte, and small intestinal changes such as mucous secreting goblet cell hyperplasia (98) and smooth muscle hypercontractility (99) associated with tissue repair mechanisms (100). In some previous studies, ILC2s are established as essential innate immune effector cells to protect against helminth infections *nippostrongylusbrasiliensis*(83).

Tuft Cells and immune resident lymphocytes (ILCs)

ILCs stimulate protecting inflammatory responses in the barrier sites in addition to tissue homeostasis. In this background, prolonge ILC activation may result in pathological outcomes after chronic inflammation (79). Promotion of type 2 response after helminths infection and allergines is not fully clear. Animal studies results reflect ILC2s as the dominant source for IL-5, IL-9, and IL-13 cytokines, and initiate type 2 inflammations. These make understanding of ILC2s activation as of high interest (101-105). However, ILC2s lack an Ag receptor, the way of the activation not depends on direct antigen recognition. Signals including cytokines (74, 75, 101), lipids (106, 107), and neuronal peptides (108-110) are integrated to induce ILC2s activation. Current studies recommend that ILC2s activation is directly affected by homeostatic disruptions of surrounding tissues (111). IL-25 production to a great or significant extent happens after helminths infection in the intestine (75, 112) which as Act1 downstream adaptor, and induce type 2 immunity to enhance worm removal (113). Worm expulsion by IL-25 is independent of Th2 function, reflecting its efficiency (76, 101). The cellular source of IL-25 was unclear till recent use of Il25-RFP reporter mice in some related researches; they proposed that tuft cells as the dominant source of IL-25 at homeostatic or protection condition in the small intestine (71, 72). Tuft cells produce IL-25 to promote tuft–ILC2 circuit activation then ILC2s derive IL-5, -9, and -13 to stimulate type 2 inflammation. Moreover, IL-13, direct tuft and goblet cells differentiation from progenitor cells in the intestinal crypts (30, 71, 72). Tuft and goblet cells rapidly respond to increasing in number around 10-folds during helminth infection. Consistent with these previous findings, recombinant IL-4, IL-13, IL-25, and IL-33 induced tuft cell hyperplasia in the small intestine. Tuft cells knockout mice (e.g., Pou2f32/2, Il252/2, and Il4Ra2/2) showed an inability to expel *Nippostrongylusbrasiliensis*(72, 114). Amazingly, systemic addition of recombinant IL-4 constitutively induces tuft cells hyperplasia only in the small intestine (115).

Tuft cells are also found to be populated in other tissues including gall bladder, pancreatic ducts, cecum, and colon, but the similar immune function has not been reported as in the small intestine. Deletion of A20 from ILC2s, activate tuft–ILC2 circuit but without type 2 inflammatory condition detected in other tissues (116). Tuft–ILC2 circuit activation through IL-4/13 signaling it seems to be exclusive of the small intestine epithelium (115). Similarly mice have been found to express IL-25R and produce IL-13, therefore, rapid removal of rodent roundworm *N. brasiliensis* from the small intestine of young, unmanipulated mice was observed. Although, IL-13 may produce from other cells, especially under the condition of chronic infection or from memory cells, ILC2s effect in the activation of tuft–ILC2 circuit may be substituted (33, 117-119).

Tuft cells as shown implicated in the process of intestinal helminths removal, also other studies revealed the importance of tuft–ILC2 circuit in protists expulsion such as *Tritrichomonas*(30). This study explained how tuft cells sense the surrounding microorganisms to induce type 2 immunity. Type 1 immune response is initiated after immune cells and intestinal epithelial cells recognize pathogen-associated molecular patterns with pattern recognition receptors. This chemosensing of microbial patterns to induce cells that mediate type 2 immunity is not well understood (48, 50, 51, 118). Tuft cells position in the outer surface of the small intestine allowed the rapid and direct sensation of luminal contents. Tuft cells hyperplasia was diminished when Trpm5$^{-/-}$ and Gnat3$^{-/-}$ mice colonized with *Tritrichomonas*. Gnat3$^{-/-}$, not Trpm5$^{-/-}$mice when colonized with helminths *N. brasiliensis* and *H.Polygyrus*tuft cell hyperplasia occurs normally suggesting distinctive tuft cells sensing for helminths and protists (120). Tuft cells lack canonical taste receptor, and that suggests other G protein-coupled receptor, predominantly, succinate receptor 1 (SUCNR1) was detected in both TRPM5^{+} and IL-25^{+} tuft cells (33, 120, 121). Succinate administration in drinking water to mice stimulated tuft cell hyperplasia in a Sucnr1-, Il25-, and Trpm5-dependent pathway (120, 121). Other features of type 2 response were also

detected such as eosinophilia, IL-13 production by ILC2s, and goblet cell hyperplasia (116, 120). Succinate is the first metabolite identified to trigger tuft cell hyperplasia and therefore mediate type 2 responses. Detection of other metabolites that may influence tuft cells hyperplasia is therefore important as stimulation of tuft cells hyperplasia results in stimulation of type 2 immune response that subsequently provide protection against type 1 diabetes.

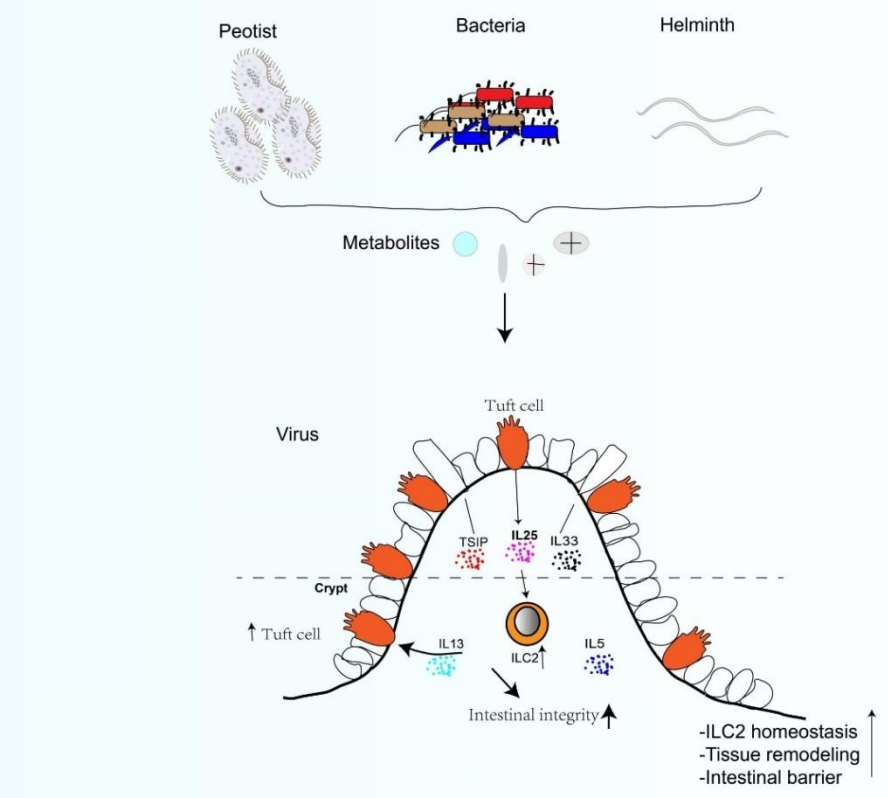

Figure1. Intestinal integrity

Scheme illustrating the intestinal microbiota metabolites mediate tuft cells-ILC2 circuit activation. This circuitpromotes ILC2 homeostasis, tissue remodeling, and intestinal barrier.

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