Tuft Cells: a new flavor in innate epithelial immunity

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Abstract

How host cells sense intestinal parasitic infection and initiate the appropriate immune response has long been a focus of many immunologists. Three new papers now identify a critical role for tuft cells, an epithelial cell involved in perception of taste, as key players that kick start Type 2 immunity.

Main text

Infection with intestinal dwelling helminths is commonly associated with the generation of type 2 immunity. The cytokine interleukin (IL-) 13 is critical in driving this characteristic 'allergic' immune response[1] and is secreted by type two innate lymphoid cells (ILC2) and CD4+T cells. ILC2 are believed to be major initiators of type 2 immunity following parasitic infection[2], although a long-standing question that still remains to be answered is how the expansion and proliferation of ILC2, via production of the key epithelial cytokines IL-33 and IL-25, is orchestrated?

Three recent papers now provide a significant advance in our understanding of this process. All have used intestinal dwelling nematodes (*Nippostrongylus brasiliensis* and/or *Heligmosomoides polygyrus*), while one study used the enteric protozoan (*Tritrichomonas muris*) as drivers of type 2 immunity. Coupled with the use of a variety of transgenic mouse strains this powerful combination has allowed a series of elegant and definitive experiments to collectively show that the expansion of ILC2s is dependent on a much-neglected epithelial cell type – the tuft cell. Although discovered 60 years ago, relatively little is known about

tuft cell (also known as brush cell) function. It has been postulated that they play a chemosensory role and indeed tuft cells encode genes involved in the transduction of bitter and umami tastes [3].

Using a "knock-in" mouse (Flare 25 – flox and reporter of *Il25*) von Moltke *et al*. [4] were able to identify that the cells in the epithelium of the digestive tract (as well as lung and gall bladder) expressing IL-25, under normal homeostatic conditions, were indeed tuft cells. Importantly, *N. brasiliensis* infected Flare 25 mice exhibited a dramatic hyperplasia of tuft cells in the small intestine, returning to homeostatic levels after worm expulsion. Infection with *H. polygyrus* was also associated with a small intestinal tuft cell hyperplasia. Further studies of *N. brasiliensis* infection in a panel of immunologically compromised mutant and transgenic mice confirmed that IL-13 was a key cytokine in tuft cell hyperplasia operating through IL-4Rα. Moreover, studies using cytokine administration *in vivo* and *ex vivo* intestinal organoids showed that IL-25 from tuft cells acted upon ILC2 to induce IL-13 production which in turn promoted further tuft cell hyperplasia in a feed-forward loop. These data suggest that waves of tuft cell hyperplasia emanate from stem cell differentiation decisions in the intestinal crypts, evident from the observed organoid tuft cell hyperplasia upon Notch signalling inhibition.

Data from Gerbe and colleagues[5] was very much in accordance with that of von Moltke *et al.* [4] published in the same issue of Nature and demonstrating a significant intestinal hyperplasia in tuft cells following helminth infection in mice. They demonstrated that tuft cells expressed the Pou domain class 2, transcription factor 3 (Pou2f3) and that Pou2f3 null mice contained no tuft cells and depressed IL-25 expression even after infection with intestinal helminths. This was also associated with a marked depression in a number of type 2 immune mediated changes, including goblet cell hyperplasia, Retnlβ expression, ILC2 expansion and IL-13 expression in intestinal tissue. Taken together, this data supports a strong link between tuft cell hyperplasia and goblet cell hyperplasia, the latter key to worm expulsion[6]. Accordingly, Pou2f3 null mice showed a highly significant delay in *N. brasiliensis* expulsion with some worms

remaining in the intestine until day 42 post infection. Organoid cultures and cytokine add back experiments using the Pou2f3 null mice confirmed that IL-13 acted downstream of the tuft cell lineage. This supported the concept of a positive feedback loop in which ILC2 expansion, driven by tuft cell derived IL-25, promoted IL-13 driven tuft cell hyperplasia with the resultant goblet cell hyperplasia driving parasite expulsion from the intestinal tract.

The paper from Howitt *et al.* [7]stemmed from observations of the number of tuft cells (Dclk1 positive cells) in the intestinal tract, as part of a study into the role of taste-chemosensory cells in recognition of intestinal microbes via G protein couple receptors. They observed that mice bred in their facility exhibited elevated numbers of tuft cells in comparison to previously published work. A series of experiments identified that this was due to the presence of the common protozoan *T. muris*. As intestinal helminths are also frequent infections of the mammalian intestine, infection by *N. brasiliensis*, *H. polygyrus* or *Trichinella spiralis* confirmed and extended the parasite driven tuft cell hyperplasia data from the other two groups. The role of tuft cells as chemosensory cells was explored using mice which lacked either the taste-specific G protein subunit gustducin, or the transient receptor potential cation channel, subfamily M, member 5 (TRMP5), a cation channel known to be important in the signaling cascade of chemosensory cells in the gut. Gustducin null mice had significantly fewer tuft cells after *T. muris* infection, while TRMP5 null mice also showed blunted tuft cell and goblet cell hyperplasia. *In vivo* cytokine and *ex vivo* organoid cultures in TRMP5 null mice showed IL-25 was produced by tuft cells and that ILC2 were a critical part of tuft cell hyperplasia through secreting IL-13. The authors concluded that the tuft cells may detect protozoans (and presumably metazoan parasites) through TRMP5 taste chemoreception to initiate the tuft cell/ILC2 feed-forward loop.

These three papers make a major contribution to our understanding of the initiation of type 2 immune responses to metazoan and protozoan enteric parasites and provide a clear link between the epithelial barrier and the innate immune response (Fig. 1). Whether this is the only function of tuft cells during

infection is unknown; tuft cells also possess the cellular machinery to influence intestinal smooth muscle contraction, blood pressure and water balance, being closely associated with nerve fibers and secreting leukotriene C4 and certain opioids [8, 9]. Also, we are still to define the precise nature of the parasite derived or infection induced molecules that are 'tasted' by the tuft cell. Regardless, these studies highlight the rich biology of 'rare' cell populations in the generation of immune responses to infection.

Figure 1. Taste your parasites. Helminth or infection induced molecules are sensed via tuft cells expressing the transient receptor potential cation channel, subfamily M, member 5 (TRMP5) and gustducin-α. In response, tuft cells release the alarmin IL-25 which increases type two innate lymphoid cells (ILC2) numbers and their secretion of the cytokine IL-13. In turn IL-13 signals to the pluripotent stem cell niche within the intestinal crypt and promotes the differentiation of tuft cells, possibly by altering Notch signaling. This tuft cell hyperplasia causes a feed-forward loop and concurrent goblet cell hyperplasia, leading to worm expulsion.

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