Giardia Muris Infection Leads to Tuft Cell Hyperplasia at Later Stages of Infection

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Introduction: Chemosensory enteric tuft cells (ETCs) can detect and respond to certain enteric parasitic infections. ETCs play important roles in modulating Th2 immune responses and in promoting parasite clearance (1,2). They can utilize various luminal surface receptors to detect their surroundings including ligands which can be supplied directly by the parasite or indirectly *via* excretory/secretory products (1,2). ETCs are characterized by the secretion of IL-25, which subsequently activates type 2 innate lymphoid cells (ILC2s), leading to tuft and goblet cell hyperplasia. To date, interactions between *Giardia*, a protozoan that causes intestinal barrier dysfunction (3), and ETCs has not been previously studied. In this study, we aim to characterise the tuft cell response to *Giardia muris* both during the acute and post-infectious phases of infection. Methods: C57BL/6 mice and tuft cell-deficient mice (*Pou2f3*$^{-/-}$) were orally gavaged with 5x10^4 *Giardia muris* trophozoites. Parasite burden was measured in the duodenum at days 4, 11, and 21 post-infection. Paraffin embedded jejunum tissue sections were stained using antibodies for doublecortin-like kinase 1 (DCLK1), a tuft cell marker, at days 4, 11, and 21 post-infection. DCLK1$^+$ cells were quantified to assess tuft cell hyperplasia. The expression of genes involved in tuft cell sensing and activity were assessed using quantitative PCR (qPCR). Results: *G. muris* infected C57BL/6 mice displayed increased levels of tuft (DCLK1$^+$) cells in the jejunum at 21 days post-infection, but not at days 4 and 11 post-infection. At 21 days post-infection, infected mice showed an increase in *Dclk1* mRNA expression. Tuft knock-out mice (*Pou2f3*$^{-/-}$) showed decreased trophozoite burden during the acute phase of infection. Interestingly, *Pou2f3*$^{-/-}$ mice did not clear the infection at day 21 (post-infectious phase), compared to WT mice. Conclusions: Upon *G. muris* infection, tuft cell levels were increased during the later stages of infection, thus ETCs may play a role in mechanisms pertaining to the clearance or repair of infection. Tuft cells may contribute to the establishment of and in the timely clearance of *Giardia* infection, however the mechanism through which tuft cells sense and respond to this environment remains to be characterised.

References:

1. Nevo S, Kadouri N, Abramson J. Tuft cells: From the mucosa to the thymus. *Immunol Lett*. 2019;210:1-9.

2. Schneider C, O'Leary CE, Locksley RM. Regulation of immune responses by tuft cells. *Nat Rev Immunol*. 2019;19(9):584-593.

3. Allain T, Amat CB, Motta JP, Manko A, Buret AG. Interactions of Giardia sp. with the intestinal barrier: Epithelium, mucus, and microbiota. *Tissue Barriers*. 2017;5(1):e1274354.