

Title: Chronic High-Fat Diet Drives Gastric Tuft Cell Hyperplasia

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Background and Aims: Tuft cells are rare chemosensory epithelial cells that play key roles in mucosal epithelial homeostasis, immune response, and tumorigenesis. While tuft cells have been widely studied in the intestine and airway, their role in the stomach remains poorly characterized. We previously found that administration of a high-fat diet (HFD) to wildtype C57BL/6J mice damages the gastric epithelium and elicits robust inflammation. We hypothesize that long-term HFD feeding results in increased IL-13 production by immune cells, which promotes tuft cell hyperplasia and contributes to the development of gastric metaplasia, a known pre-cancerous lesion.

Methods: C57BL/6J mice were fed a control or HFD for 26 weeks. Gastric tissue was collected for histological and immunofluorescent analyses.

Results: HFD-fed mice showed pronounced gastric epithelial remodeling compared with control-fed mice, including tuft cell hyperplasia and gastric metaplasia. In the intestine, tuft cells have been recently clustered into two classes based on transcriptomic profiles, with type 1 tuft cells exhibiting a neuronal associated gene signature and type 2 tuft cells being enriched in immune response related genes. In the stomach, we found that HFD-induced injury led to a significant increase in neuronal-associated type 1 tuft cells and immune-associated type 2 tuft cells. Tuft cells, normally confined to the neck of the gastric gland in control-fed mice, redistributed throughout the gland in HFD mice. We observed an increased prevalence of tuft cells at the base and middle of the gland in mice fed an HFD. Spatial distribution analysis demonstrated that expansion of neuronal-associated type 1 tuft cells was localized to the base of the glands, while immune-associated type 2 tuft cells expanded throughout the gland. Gastric tuft cells also underwent distinct morphological changes, including changes in size and shape. Immunostaining for immune cells and for IL-13 demonstrated a significant increase in immune cell derived IL-13 in HFD. IL-13 is known to drive tuft cell expansion in other organs and is likely a key driver of the tuft cell hyperplasia that we observed in our HFD gastric injury model.

Conclusion: Our data demonstrates that tuft cells are expanded during HFD induced gastric injury. Collectively, these data suggest that chronic dietary injury impacts tuft cell number and structure, with implications for gastric malignancy.