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ENVIRONMENTAL CUES SHAPE MUCOSAL ENTERIC GLIA HOMEOSTASIS INDEPENDENTLY FROM VAGAL INNERVATION

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Mucosal enteric glia are a sub-population of enteric glia residing in the intestinal lamina propria, where they closely associate with both intrinsic (enteric) and extrinsic (vagal afferent) neuronal processes. Characterized by type-III morphology, these cells are implicated in different aspects of epithelial function (*Prochera et al, Neuroscience letters, 2023*), such as Paneth cell secretion, intestinal stem cell maturation and entero-endocrine activity. Interestingly, their presence in the lamina propria is regulated by the microbiome as germ-free and antibiotic-treated mice display a reduced density of mucosal enteric glia, which is re-established once microbiota are restored (*Kabouridis et al, Neuron, 2015*). However, the mechanisms that dictate their presence and govern their migration in the mucosa remain obscure. We hypothesize that mucosal enteric glia depend on environmental cues and require mucosal innervation for their colonization of the lamina propria and maintenance in intestinal villi.

The positioning, density and morphology of mucosal enteric glia were analyzed in whole mounts of the small and large intestine in different mouse models (conventional laboratory mice receiving a wheat-based or soya-based diet, germ-free mice and wildling mice), employing *Sox10-Cre^{ERT2};Ai14* reporter mice and immunostaining for Sox10 and S100β. In addition, to investigate their dependence on lamina propria innervation, mucosal enteric glia were examined in surgical models of sub-diaphragmatic vagotomy in conventionally raised mice and conventionalized germ-free mice. *vGlut-Flp;Phox2B-Cre;Ai65* mice were used to validate the vagotomy experiments.

In line with earlier reports, we observed a consistent decrease in mucosal enteric glial density in both the small and large intestine of germ-free mice, alongside alterations in their morphology. Moreover, we found region-specific variations in glial density and cyto-architecture in the colon of Wildling mice and a general increase of glial density in the whole intestine of mice fed with a soia-based diet. Neither unilateral, nor bilateral sub-diaphragmatic vagotomy affected the density or positioning of mucosal enteric glia in the lamina propria. Furthermore, unilateral subdiaphragmatic vagotomy did not influence the colonization of the lamina propria induced by conventionalization of germ-free mice.

Characterizing mucosal enteric glia along the gastrointestinal tract, we provide new insights into their interactions with the microbiome, diet and lamina propria innervation. Our work suggests that mucosal enteric glia colonization and presence in the lamina propria doesn't rely on vagal innervation, opening new perspectives for investigating their physiology.