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MIRNA-DRIVEN GLIOSIS: UNRAVELLING THE ROLE OF MIR-146A-5P IN ENTERIC GLIAL REACTIVITY

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Enteric glial cells, a heterogeneous population of peripheral neuroglia located in the gut wall, play important roles in gastrointestinal physiology. In response to tissue damage and inflammatory cues, enteric glia acquire a reactive phenotype, shaping the immune environment and affecting disease progression. However, the molecular mechanisms regulating enteric glia reactivity are incompletely understood. microRNAs, via post-transcriptional control of gene expression, shape cellular phenotypes during homeostasis and disease. Our preliminary data indicates that distinct miRNA profiles mark enteric glial status and suggest the involvement of miR-146a-5p in regulating enteric glial reactivity. Aiming to elucidate miR-146a-5p-mediated regulation of enteric glial plasticity, we combine primary enteric glial cell culture experiments, in silico target gene analyses and in vivo mouse assays. First, using an in vitro model of enteric gliosis instructed by lipopolysaccharide and interferon gamma treatment, causing morphological changes and upregulation of proinflammatory markers, we found elevated miR-146a-5p transcript levels in reactive enteric glia. This was validated in silico by target gene analyses, highlighting miR-146a-5p's involvement in pathways linked to gastrointestinal disorders characterized by enteric glial cell plasticity. Conditional inactivation of miR-146-5p in enteric glial cells using Sox10-CreERT2 mice did not impact enteric nervous system (ENS) organization or gut function during steady-state conditions. Currently, studies on the role of enteric glial miR-146a-5p in an in vivo model for intestinal inflammation (colitis) are ongoing. In this model, enteric glia-specific miR-146a-5p deficient mice are administered 3% Dextran Sulphate Sodium via the drinking water, and after 8 days, disease activity, intestinal histopathology, gut function and ENS structure will be assessed. Aiming to disentangle the molecular mechanisms sculpting enteric glia reactivity, these experiments are complemented with in vitro assays involving gain- and loss-of-function approaches tailored for the modulation of miR-146a-5p levels in primary enteric glial cell cultures. Our data suggest that miR-146a-5p does not play a determinant role in enteric glia function at steady state but that its expression is associated with enteric glia reactivity. Our ongoing experiments will explore the effects of miR-146a-5p modulation on enteric glial status and unravel the role of enteric glial miR-146a-5p during intestinal inflammation.