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Neuronal Specification in the Enteric Nervous System

Ulrika MARKLUND

Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Sweden

Email: ulrika.marklund@ki.se

The enteric nervous system (ENS) organizes into irregular ganglia of intermingled neural types spanning the entire length of the gut. Meticulous work has identified various enteric neural phenotypes, but lack of unique molecular markers has hampered elucidation of the full cellular complexity. My lab aims to determine the cellular makeup of the ENS at a molecular and circuit level, and reveal how the diversity emerges during the embryonic development. We have characterized the ENS of mouse gastrointestinal tract during juvenile and embryonic stages using single cell RNA-sequencing combined with histochemical technologies and analysis of mutant and transgenic mice. Analysis of the myenteric plexus identified 12 enteric neuron classes in the small intestine and through further analysis of class-specific Cre mice we have begun to map their morphologies, innervation pattern and connectivity[1]. Notably, several gut disorders are characterized by the dysfunction of selective enteric neuron types and these disorders may be emendable to cell replacement therapies. Such treatment would necessitate in depth knowledge of the molecular underpinnings to neuron identity formation in the developing ENS. Although different enteric neurons have been found to emerge in a temporally ordered sequence during the development, the underlying molecular mechanisms remain unclear. Our transcriptome analysis of the developing myenteric ENS revealed a step-wise diversification process, in which stem cells first undertake a binary decision followed by further diversification at the postmitotic stage. Extending our characterization into the later formed submucosal plexus we found only 3 cardinal neuron types, that were transcriptional siblings of late-generated myenteric neurons and formed through similar mechanisms[2]. We propose a unified developmental framework governing enteric neuron development across the gut wall, where temporal emergence combined with binary neurogenic fate decisions defines the identities of enteric neurons.

References:

1) Morarach K et al., Diversification of molecularly defined myenteric neuron classes revealed by scRNA-sequencing. Nature Neuroscience 2021. Doi:10.1038/s41593-020-00736-x
2) Li et al., The transcriptomes, connections and development of submucosal neuron classes in the mouse small intestine. Nature Neuroscience 2025 doi: 10.1038/s41593-025-01962-x