

# Cellular signalings underlying the interplays between enteric neuronal progenitors and mesenchymal cells during bowel development

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Hirschsprung disease (HSCR) is a congenital disorder of the colon characterized by the absence of specific nerve cells due to incomplete colonization of the bowel by enteric neural crest cells (ENCCs). This condition leads to functional intestinal obstruction. Stem cell therapy shows promise as a potential treatment option for HSCR. However, despite significant advancements in identifying suitable cell sources and developing transplantation strategies, our understanding of the molecular mechanisms essential for forming a functional neuronal network in the bowel remains limited. This knowledge gap has significantly impeded progress toward effective cell replacement therapies for HSCR.

Vinculin (VCL) is an adaptor protein crucial for focal adhesions, as it integrates various external signals and facilitates cell-cell communication, positioning it as a potential hub gene in the development of the enteric nervous system (ENS). In this study, we aimed to create a comprehensive map of the signaling pathways involved in the formation of the ENS, utilizing neural crest-specific Vcl knockout mouse mutants (Vcl cKO).

Loss of Vcl severely disrupted cell-cell interactions among ENS cells, resulting in delayed gut colonization and failure in ganglionogenesis. Subsequent high-resolution transcriptomic analysis reconstructed the differentiation trajectory of ENCCs along the neuronal lineage development, revealing that genes associated with axonogenesis are dysregulated in ENS cells, along with compromised cellular signaling pathways. Additionally, spatial RNA sequencing indicated that ENS-mesenchyme interactions are reduced in the Vcl cKO gut, and it was found that the pleiotrophin (Ptn) pathway is significantly dysregulated during the development of the ENS in Vcl cKO. Notably, Ptn knockout (KO) mutants consistently exhibited abnormal ganglionogenesis, highlighting the complex interplay between ENS and mesenchymal cells that guides various steps of ENS network formation.

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Dear Elly Ngan

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We look forward to welcoming you to Istanbul!

Kind regards,

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