(T1239) Elucidating the Roles of Intestinal Niche Factors and their Interactions in Hirschsprung Disease Through Integrated Analysis

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Abstract: Hirschsprung disease (HSCR) is a congenital disorder characterized by the absence of ganglion cells in the distal colon. Autologous or allogenic transplantation of enteric progenitor cells/neurons are considered as promising regenerative therapies for HSCR. However, the migration, differentiation, and functional integration of the grafted progenitor cells into the host gut are highly dependent on the interaction with the intestinal neural stem cell niche constituting the postnatal gut microenvironment. To date, the essential intestinal niche factors required for enteric neural crest cell migration and differentiation remain largely uncharacterized. In this study, we conducted a pilot integrated analysis of whole-genome sequencing (WGS) and bulk RNA sequencing (RNA-seq) on aganglionic and ganglionic colonic segments of a small cohort of HSCR patients to identify the molecular signatures characterizing the niche environment of the colon of HSCR patients. The comparison of expressions in gene and transcript level between aganglionic and ganglionic segments revealed a related set of differentially expressed genes (DEGs). Enrichment analysis of the DEGs further emphasized signaling pathways pertinent to enteric nervous system development and function. In addition, scRNA-seq of colonic tissues from HSCR patients, including neuronal cells and other cell types, demonstrated complementary insights, showing the granularity of gene expression changes in individual cell populations. Moreover, to better understand the factors guiding early ENS development, we also employed a scRNA-seq dataset of mouse embryonic ENS models and through this model we analyzed cell-cell interactions and characterized the expression of key markers in the early stages of ENS generation—insights that can inform how transplanted cells might integrate into the gut in human HSCR. By integrating WGS, RNA-seq, and scRNA-seq datasets, this study provides a glimpse into the potential intestinal niche factors dysregulated in HSCR patients.

Funding Source: Thanks to Theme-based Research scheme [grant number T12C-714/14-R], FDCT [grant number 0097/2022/A2], REACH research grant, Health Medical Research Fund (HMRF) [grant numbers 06171636, 08193446, PR-HKU-1 and 08191496].