A078 · Sn-seq analysis reveals distinct pathway programs in Gpr149+ vs GPR149- Medium Spiny Neurons in Parkinsons Disease

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G protein-coupled receptor-149 (GPR149) is a class A orphan receptor highly expressed in the basal ganglia (BG). Our previous analyses linked GPR149 expression to dopamine signaling networks, suggesting a potential role in BG function. Given the role of BG dysregulation in disorders like Parkinson's disease (PD), we investigated whether GPR149 contributes to PD pathogenesis by generating a single-nucleus RNA-seq atlas from healthy donor BG to understand baseline expression patterns. We observed that GPR149 is primarily enriched in striatal medium spiny neurons (MSNs) and is associated with decreased cyclic-AMP signaling, as indicated by gene set enrichment analysis (GSEA). Next, we compared these findings with a two-cohort PD dataset (n=106). Our findings were significantly replicated in the MSNs from healthy controls in the PD cohort, at both the gene and pathway levels (assessed using hypergeometric and Jaccard overlap statistics across the DE and KEGG enrichment lists). Next, PD-associated transcriptional responses were modeled separately within GPR149+ and GPR149- MSNs using donor-level pseudobulk analyses adjusted for cohort. GSEA and DE comparing PD versus control within GPR149+ and GPR149- MSNs revealed largely distinct molecular signatures. The GO biological process enrichment showed minimal overlap and statistically indistinguishable results (Jaccard's similarity and hypergeometric tests) between the two populations. KEGG enrichment analyses yielded similarly minimal overlap across multiple FDR thresholds. Together, these findings suggest that GPR149+ and GPR149- MSNs engage distinct pathway programs in PD. Future studies using MSN-specific gene knockout mice and striatal PD organoids can determine if GPR149 confers neuronal vulnerability or protection during disease progression.