Modeling LEPID Pathogenesis in vitro: siRNA Knockdown of Kars1 in PC12 Cells Reveals Downstream Gene Dysregulation

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KARS1 encodes bifunctional cytoplasmic and mitochondrial lysyl-tRNA synthetases, and biallelic loss-of-function variants cause infantile-onset progressive leukoencephalopathy (LEPID) and related neurodevelopmental disorders. However, the downstream transcriptomic effects of KARS1 deficiency in mammalian neural cells remain incompletely defined. In this study, siRNA-mediated knockdown of Kars1 in undifferentiated rat PC12 cells was used to model KARS1 loss-of-function in a neuronal context. Quantitative PCR (qPCR) confirmed suppression of Kars1 mRNA and assessed expression changes in a curated panel of downstream candidate genes (Stxbp1, Atp2b1, Scamp5, Hspd1, and Casp8) involved in mitochondrial homeostasis, myelin integrity, synaptic vesicle cycling, calcium handling, and stress-response pathways. Consistent dysregulation of these genes following Kars1 knockdown prompted subsequent RNA sequencing, which revealed that many of the most differentially expressed genes were linked to neurodevelopmental phenotypes and pathways essential for neuronal survival and function. These findings support a model in which KARS1 deficiency disrupts mitochondrial and proteostatic balance in neurons, leading to impaired myelin and synaptic function that may contribute to LEPID and related disorders. By mapping these transcriptomic changes, this work helps identify potential molecular targets for understanding and eventually treating KARS1-associated diseases.

Awards Won:

Third Award of $1,200