Using human Induced Pluripotent Stem Cell derived neural lineages to model Thyroid Hormone Signaling

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Background

Thyroid hormone (TH) is essential for normal human brain development. Untreated congenital hypothyroidism or disorders due to defects in TH signaling result in severe neurodevelopmental problems. Mouse models of TH-related disorders of human brain development fail to recapitulate critical aspects of the pathophysiology, and human cellular models have not yet been established. Therefore, we sought to leverage human **induced Pluripotent Stem Cell (iPSC) technology** for modeling **TH physiology in human neural cells**.

Objective

We aim to understand the basic properties of TH regulation in defined human neural cell types.

Methods

We generated defined central nervous system cell types from human iPSCs: Neurons, astrocytes, Neural Precursor Cells (NPCs) and Oligodendrocyte Precursor Cells (OPCs) by using **cell type-specific-differentiation protocols**. We performed T3 and T4 **transport assays** and **deiodinase assays**, as well as **qPCR, Western Blotting and Immunocytochemistry,** to quantify the expression level of genes, which have crucial role in TH signaling.

Results

We characterized the baseline rates of T3 and T4 transport and metabolism in defined neural cell-types. **Uptake of THs varied across cell types, with OPCs showing the highest accumulation of intracellular T3.** Transport studies with the addition of the MCT8-specific inhibitor Silychristin suggests **MCT8-dependent uptake** in all lineages. **High D3 activity** was seen in NPCs and astrocytes, but D3 activity was undetectable in OPCs. No D2 activity was observed in any of the cell types examined. In addition, we confirmed the expression of TH signaling genes by qPCR, Western Blotting and Immunocytochemistry.

Conclusions

Our results indicate that distinct neural cell lineages have a unique combination of TH signaling features. Defined neural cell lineages differentiated from human iPSCs provide a unique tool to model TH physiology and disorders associated with disrupted TH signaling.