

Differentiation of neural progenitor cells (NPCs) into neurons is a highly orchestrated and complex process. Recent findings indicate a fundamental role of mitochondria in regulation of the NPC fate decisions. In order to maintain mitochondrial health and facilitate proper functioning of neuronal cells, excessive or defective organelles are eliminated by the process of mitophagy. This process has been shown to be essential in maintaining mitochondrial health, thus facilitating proper functioning of neuronal cells and, as recent findings indicate, neural cell fate commitment.

Integrated Nuclear FGFR1 Signaling (INFS), governed by nuclear FGFR1, orchestrates genomic reprogramming during the transition from embryonic to neuronal cells. Genomic studies revealed that nuclear FGFR1 binds to the promoters of genes involved in pluripotency, neuronal differentiation, axonal guidance as well as the key genes involved in mitochondrial biogenesis and mitophagy. Moreover, the author's recent transcriptomics data revealed that FGFR1 inhibition elevates genes crucial for mitochondrial dynamics and mitophagy (*PPARGC1A*, *FIS1*, *OPA1*, *OPTN*, *SQSTM1*, *PHB2*, *HTRA2*) which suggests that FGFR1 is directly involved in these processes.

This project attempts to uncover the interplay of nuclear FGFR1 and mitophagy in neural stem cell type specification during human cerebral cortex development. To address this question, a human cortical organoid model derived from human induced pluripotent stem cells (iPSCs) will be used. 3D cortical organoids recapitulate spatial organization, neural layering and cytoarchitecture similar to the second trimester of human brain development. Therefore, cortical organoids, derived from human induced pluripotent stem cells (hiPSC), can be used to decipher the impact of mitophagy on the development of the nervous system without any ethical concerns.

In this project, a stable, bicistronic reporter iPSC line will be obtained to monitor mitophagy flux and conditionally control expression of nuclear FGFR1 throughout cortical organoid development. Mitophagy activity will be modulated by pharmacological inhibition and conditional overexpression of nuclear FGFR1, and its effect on neural cell type specification will be evaluated at later stages of cortical organoid development.

Changes will be determined by the analysis of expression of genes involved in mitochondrial biogenesis, mitophagy and neural differentiation. Whole transcriptomics analysis will be used to uncover the regulatory mechanisms underlying the role of INFS on mitophagy during early neural cell commitment. This approach will allow to determine whether the interplay between mitophagy and INFS has an impact on neural cell type specification at later stages of cortical organoid development. We expect that suppression of mitophagy by nuclear *FGFR1* at early stages of neurogenesis will induce proliferation of neural stem cells and their further cell type specification during human cortical organoid development.

This project will contribute to expanding the basic knowledge of understanding the role of mitophagy in neural development in the early stages of human brain development. Uncovering the regulatory mechanisms of mitophagy can lead to the development of novel therapies for neurodevelopmental and neurodegenerative diseases.