Investigating the role of SQSTM1 (p62) in mitochondrial function and clearance in cortical neurons

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Introduction

Mitochondrial dysfunction is a common feature of numerous neurodegenerative diseases. Furthermore, several disease-associated mutations have been identified in genes regulating the selective degradation of damaged mitochondria by autophagy (aka mitophagy), suggesting the involvement of mitophagy in driving disease pathogenesis. Selective mitophagy is critically important for neuronal survival as it maintains an optimal cellular energy production whilst avoiding the toxic accumulation of damaged dysfunctional mitochondria, which can lead to cell death. The discovery of mutations in the PINK1 and PARK2 (Parkin) genes in Parkinson’s disease has facilitated mechanistic understanding of the mitophagy process. For inducing selective mitophagy, PINK1 and PARK2 interact with various autophagic adapter proteins including SQSTM1 (p62), which has been shown to be mutated in patients with frontotemporal dementia (FTD). The precise role of SQSTM1 in mitochondrial function and clearance remains to be clarified. In particular, it is unclear whether SQSTM1 is essential in neuronal mitophagy. To address this knowledge gap, we are assessing the importance of mitophagy in human iPSC derived neurons with or without genetic alterations in SQSTM1.

Result 2: Generation of iPSCs lacking SQSTM1

Result 3: The differentiation capacity of iPSCs into cortical neurons appears unaffected by the loss of SQSTM1.

Result 4: Depletion of SQSTM1 does not appear to significantly alter mitochondrial biogenesis and distribution in iPSC-derived cortical neurons.

Result 5: Depletion of SQSTM1 results in reduced expression of genes involved in the respiratory chain and impairs mitochondrial respiration in human iPSC-derived cortical neurons.

Result 6: Depletion of SQSTM1 reduces autophagy flux with less LC3-II accumulation in iPSC-derived cortical neurons following autophagy inhibition.

Result 7: Mitochondrial PINK1 recruitment and loss of mitochondria in iPSC-derived cortical neurons occur in the absence of SQSTM1 following mitochondrial depolarization.

Conclusions and Future Direction

SQSTM1 is a regulator of mitochondrial respiratory chain function. Despite its important role in autophagy, SQSTM1 is not essential for the clearance of damaged mitochondrial mitochondria.

Future work will examine other arms of the autophagy pathway and cargo removal mediated by SQSTM1 in our human neuronal model.

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