Impaired Mitochondrial Translation or Transcription Models Alzheimer's Disease-Like Molecular Phenotypes

Anysja Roberts, MS[1,2], Lesya Novikova, PhD[1,2], Ian Weidling, PhD[1,2], Xiaowan Wang, PhD[1,2], Emily Schueddig, MS[1] , Heather Wilkins, PhD[1,2], Dong Pei, PhD[1,2], and Russell Swerdlow, MD[1,2].

[1]University of Kansas Medical Center, [2]KU Alzheimer's Disease Research Center

Abstract

- Aging is associated with reduced mitochondrial function and an increased risk of developing Alzheimer's disease (AD). Impaired mitochondrial translation and transcription are possible mechanisms that drives mitochondrial dysfunction.
- Chloramphenicol blocks mitochondrial ribosomes, impairing translation. Inhibitor of mitochondrial transcription 1 (IMT1) impairs RNA polymerase, mitochondrial (POLRMT) is a key regulator of mitochondrial transcription.
- We hypothesize **inhibiting mitochondrial transcription, and translation** will drive mitochondrial dysfunction and **model AD.**

Objective

Impair mitochondrial translation or transcription in iPSC-derived neurons to investigate if **mitochondrial dysfunction drives AD-like phenotypes**

Methods

Cell Culture: iPSC neurons were treated for 2-weeks with 200 µg/mL CHL to block translation or 0.5 µM IMT1 to block transcription.
Data Collection and Preparation: Bulk RNA sequencing – STAR Alignment and Salmon Transcript Quantification, Mass spectrometry
Data Analysis: DESeq2 (transcriptomics) or LIMMA analysis (proteomics), and gene set enrichment analysis (GSEA). GO, Reactome, Hallmark, and MitoCarta pathway analysis.

Results

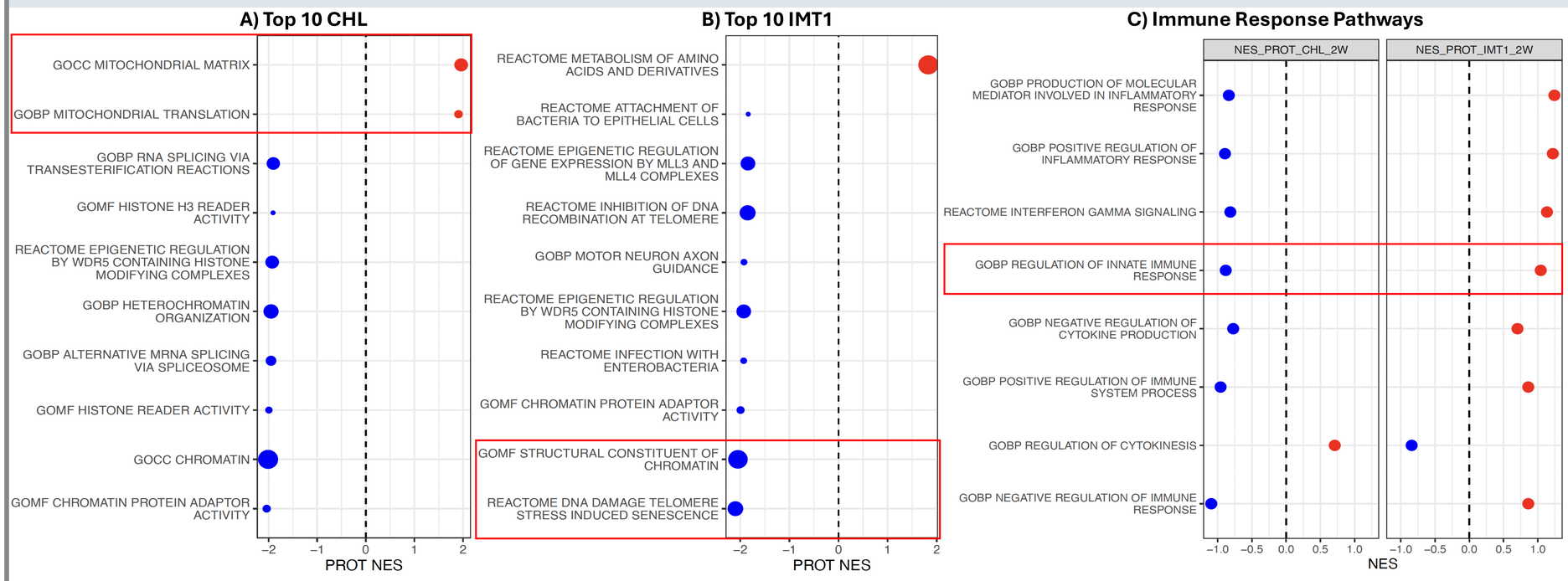

Figure 1: Top Protein Pathway changes after 2 Weeks Treatment A) Top 10 CHL Pathways, B) Top 10 IMT1 Pathways, C) Top Immune Response Pathways. Red: Up Regulated, Blue: Down Regulated

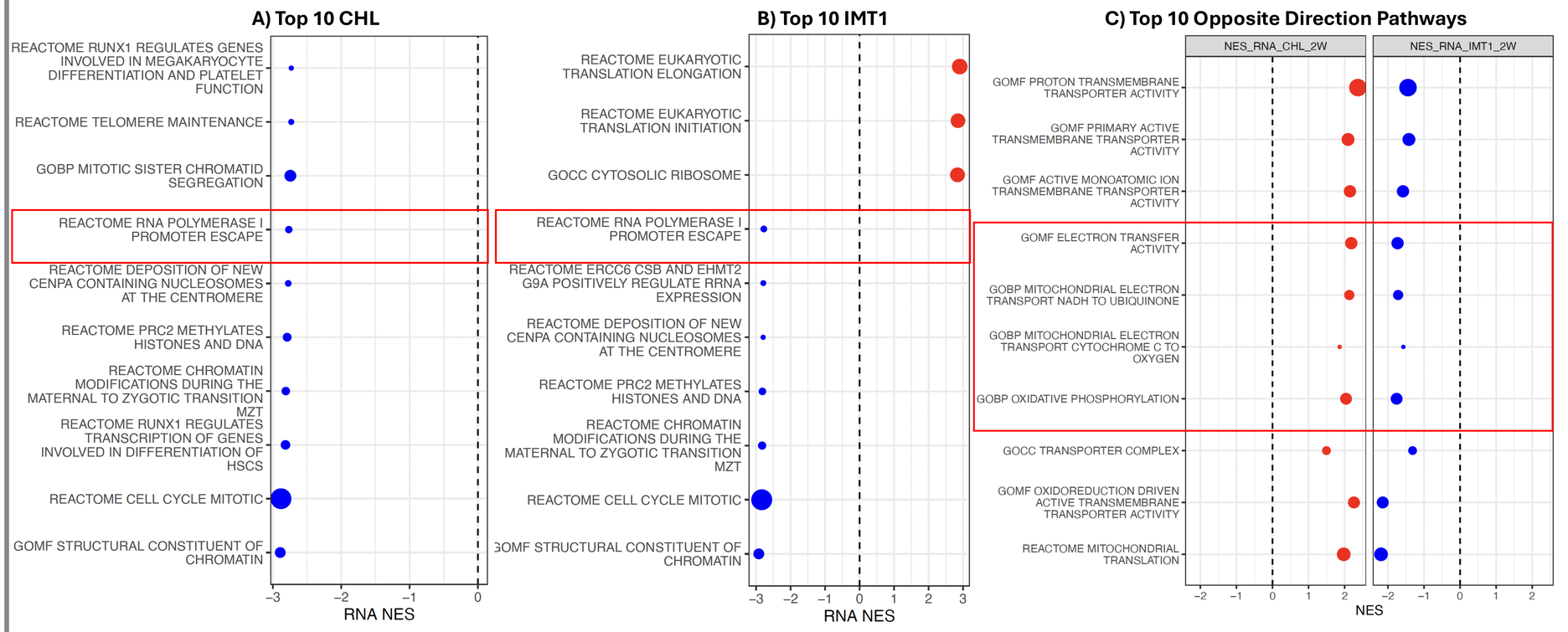

Figure 2: Top RNA Pathway changes after 2 Weeks Treatment A) Top 10 CHL Pathways, B) Top 10 IMT1 Pathways, C) Top 10 Opposite Direction Pathways. Red: Up Regulated, Blue: Down Regulated.

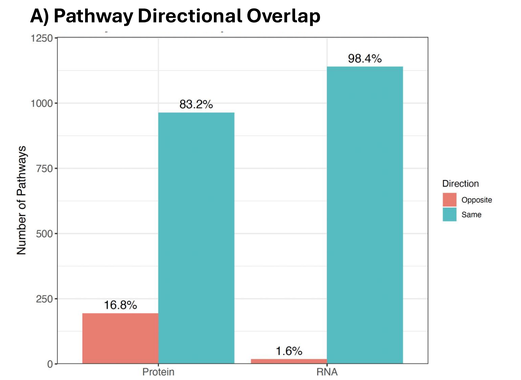

Figure 3: Concordant and Discordant Changes in CHL vs. IMT1. A) Pathway Level Changes, B) Protein/Transcript Level Changes. Orange: Concordant, Blue: Discordant

Discussion

- IMT1 and CHL have concordant changes at the transcript level and more discordant direction changes at the protein level.
- IMT1 reduces mitochondrial transcripts with CHL increases them.
- IMT1 activates immune response and CHL suppresses it

Future Work

- Compare IMT1 and CHL treatments to AMP-AD patient datasets.
- Assess the mechanism behind why IMT1 triggers the ISR while CHL dampens it.
- Generate a POLRMT knockout in iPSC neurons.

Acknowledgements

AG072973, AG060733, AG061194, Stop Alzheimer's Now Foundation, and the Biomedical Research Training Program at the University of Kansas Medical Center