Society for Developmental Biology 82nd Annual Meeting
July 20-23, 2023 | Chicago, IL

ABSTRACT BOOK

**Program Abstract #562**

# Hcfc1a, an ortholog of HCFC1, regulates brain development and Akt/mTor signaling.

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Missense mutations in the HCFC1 gene cause methylmalonic acidemia homocysteinemia, cblX type (cblX). cblX is an X -linked recessive metabolic disorder characterized by defects in cobalamin metabolism (vitamin B12), nervous system development, intellectual disability, brain malformations, and movement disorders. HCFC1 encodes a transcriptional co-activator that regulates the expression of over 5000 downstream target genes in humans, some of which are known to regulate vitamin B12 metabolism. Because of the diverse number of downstream target genes, the molecular and cellular mechanisms underlying cblX have been difficult to elucidate. We developed two germline mutations in the zebrafish hcfc1a gene, a missense and a nonsense, to explore the mechanisms by which mutations in the HCFC1 kelch protein interaction domain result in abnormal brain development. Previous studies have demonstrated the nonsense mutations cause an increase in neural precursor proliferation, which is associated with changes in the expression of the asxl1 gene. asxl1, encodes a polycomb protein known to activate Akt, a major pathway regulating cell proliferation. Based on these data, we sought to characterize the cellular and molecular phenotypes in a missense mutant of Hcfc1a, the type of mutation known to cause cblX syndrome. Missense mutation of Hcfc1a caused an increase in neural precursors (Sox2+), but a decrease in the number of radial glial cells (Gfap+). Abnormal radial glial cell number was not attributed to reduced cell proliferation or survival. Concurrently, we observed that missense mutation of Hcfc1a resulted in reduced Akt/mTor signaling. Collectively, these data suggest a function for Akt/mTor in radial glial cell development. In future studies we will create genetic knock-in alleles of patient variants to understand the role of Akt/mTor in cblX and related disorders. Funding provided by award number 1R03DE029517-01A1, 5U54MD007592, and RL5GM118969. TL4GM118971, and UL1GM118970