Elucidating the Impact of ACLY Deficiency and Global Hypoacetylation on Metabolic and Splicing Dysfunctions in Familial Dysautonomia

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Abstract:

Familial Dysautonomia (FD) is a rare neurodevelopmental disorder caused by a splicing mutation in the IKBKAP/Elp1 gene, which leads to altered pre-mRNA splicing and the production of a truncated and unstable Elp1 protein. Elp1 is a critical component of the Elongator complex, a key player in essential cellular functions, including transcriptional regulation and tRNA modification. Deficiency in Elp1 destabilizes the Elongator complex, impairing a number of cellular processes involving neuronal maintenance and function. Our previous studies suggest that FD models experience disruptions in axonal transport, partly due to the destabilization of ATP-citrate lyase (Acly), an enzyme responsible for generating acetyl-CoA. Reduced acetyl-CoA levels lead to global protein hypoacetylation, which adversely affects many cellular processes. This study aims to explore how Acly deficiency and the resulting global hypoacetylation influence both metabolic and splicing dysfunctions in FD models. Preliminary results support the hypothesis that globl hypoacetylation affects metabolic pathways, disrupting mitochondrial function and energy production in FD cells. Specifically, Acly deficiency may impair critical metabolic pathways such as TCA cycle and lipid biosynthesis, further contributing to mitochondrial dysfunction and reduced cellular energy production. Additionally, we will investigate how acetyl-CoA depletion impacts alternative splicing by examining the acetylation status of splicing factors such as hnRNP A1 and histones. We will focus on splicing patterns of key genes related to hnRNP A1 function such as MAPT (tau), pyruvate kinase and abnormal Elp1 splicing following the FD mutation, and how they response to changes in acetyl-CoA levels. We will assess the effects on FD phenotypes and cellular functions by modulating acetyl-CoA levels in cells under glucose starvation conditions, HDAC inhibitors, or direct or indirect ACLY activity modulation using diverse specific molecular agents. We will additionally analyze these effects on global hypoacetylation in our FD models by performing parallel OMICS analyses like proteomics/acetylomics, metabolomics and NGS-RNAseq. Our findings will provide new insights into the molecular mechanisms of FD, offering potential therapeutic strategies for restoring metabolic regulation, splicing activity, and axonal function.