Elucidating the Elongator Complex mechanism on global hypoacetylation in Familial Dysautonomia

Yuval Kleinberg, supervisor: Prof Miguel Weil

The Elongator complex is a multi-subunit protein assembly essential for tRNA modification, cytoskeletal remodeling, and intracellular transport. Mutations or depletion of Elongator components, particularly Elp1, are associated with neurodevelopmental and neurodegenerative disorders such as Familial Dysautonomia (FD). The loss of Elongator function results in defects in neurite formation, microtubule stability, and axonal transport, suggesting a broader role in neuronal homeostasis. We hypothesize that Elongator depletion leads to global protein hypoacetylation by impairing ATP-citrate lyase (ACLY), a key enzyme in acetyl-CoA biosynthesis. This decreases acetyl-CoA availability, affecting acetylation-dependent processes, including Tau stability and microtubule dynamics, ultimately disrupting neuronal function. Preliminary results of Proteomic and metabolomic analyses of SH-SY5Y Elp1-knockdown (Elp1-KD) cells reveal reduced ACLY levels and activity, leading to lower acetyl-CoA production and global protein hypoacetylation. In addition, treatment with a novel ACLY activator rescues neurite morphology and axonal transport defects and the levels of several relevant proteins. This study aims to identify novel molecular mechanisms underlying Elongator-associated neuronal integrity and transport and explore ACLY activation as a therapeutic strategy to restore the abnormal cellular phenotype for FD and Elongator-related disorders.