Presenter: Li Xie

Authors: LI XIE, SUN YU, GARRICK SALOIS, KELSEY WILLIAMS, CHRIS PROSCHEL

Title: DECIPHERING EIF2B5 DEFICIENCY IN VANISHING WHITE MATTER DISEASE

Abstract

Vanishing White Matter Disease (VWM), is a devastating disease associated with mutations in the translation initiation factor 2B (EIF2B), an essential factor for translation initiation. Unfortunately, due to the lack of a translational experimental model for capturing VWM disease, elucidation of the effects of EIF2B mutations on the biology of human neural cell populations within this disease has been unsuccessful. To assess whether the disease phenotypes are dependent on EIF2B activity and shared amongst different EIF2B5 mutations, syngeneic pluripotent stem cell (PSC) lines were generated using CRISPR editing. Differentiation of glial spheres from PSCs revealed reduced spontaneous astrocyte generation in mutant cells. Additionally, the mutant astrocytes displayed an abnormal morphology compared to their syngeneic controls, a finding consistent with clinical observations. Furthermore, the observation of different degree of impairment in astrocyte differentiation between the milder and more severe EIF2B5 mutants reflected the severity of VWM. To further understand whether EIF2B5 mutations impair eIF2B enzymatic activity and lead to translational defects, translatome analysis through ribosome profiling was conducted on PSCs. Result revealed that the more severe mutation generated more differentially translated genes (DTGs) compared to the milder mutation. Analysis of the DTGs demonstrated that EIF2B5 mutations selectively suppressed the translation of mRNAs with stable secondary structures in their 5` untranslated regions. In summary, I have established a novel glial sphere model to study VWM disease, which faithfully recapitulated the astrocyte impairments observed in patient tissue. My results illustrated that mutations in EIF2B5 impair spontaneous astrocyte differentiation, which is possibly a result of selective alterations in translation. Moving forward, we are intrigued to understand how selective impairment of translation in VWM mutants could contribute to the differentiation deficiency in astrocytes.