World Academy of Science, Engineering and Technology
International Journal of Medical and Health Sciences
Vol:18, No:08, 2024

iPSC-Derived Brain Organoids To Study The Mechanisms Underlying Disease Variability In Patients With SYNGAP1-Intelectual Disability

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Abstract : Rare neurodevelopmental disorders (RNDDs) encompass a spectrum of conditions affecting a minority of the global population, yet pose significant challenges due to their heterogeneity and limited understanding. Among these disorders, SYNGAP1 mutations contribute to a range of cognitive impairments, autism spectrum disorder (ASD), and epilepsy. Despite their rarity, SYNGAP1-related disorders manifest with varying severity, underscoring the need for improved insights into their underlying biological mechanisms. This research project aims to elucidate the molecular pathways driving the heterogeneous disease severity observed in individuals with SYNGAP1 mutations. Leveraging advancements in the study of extracellular vesicles (EVs), particularly their role in intercellular communication, we explore the potential of EV mRNA profiles as biomarkers for assessing brain pathology associated with SYNGAP1-related disorders. Employing a multi-faceted approach, we first characterize SYNGAP1-induced pluripotent stem cells (iPSCs) and iPSC-derived brain organoids, comparing them with familial neurotypically-developed (NTD) controls. Subsequently, we identify molecular signatures of intellectual disability (ID) and epilepsy using single-cell RNA sequencing, shedding light on the pathological mechanisms underlying these conditions. Furthermore, we investigate the feasibility of utilizing EVs as biomarkers by assessing brain-specific mRNA transcripts in blood-derived EVs from SYNGAP1 patients. Our findings suggest that EV mRNA profiles may serve as indicators of transcriptional activity in the brain, offering a non-invasive method for monitoring pathological changes associated with neurological disorders. Finally, we evaluate the efficacy of anti-seizure drugs on SYNGAP1 organoid models, leveraging MaxWell high-density microelectrode array (HD-MEA) recordings to assess electrical activity and synaptic function. This comprehensive approach aims to enhance our understanding of SYNGAP1-related disorders and pave the way for personalized treatment strategies tailored to individual patients.

Keywords : SYNGAP, autism, organoids, neurodevelopment
Conference Title : ICA 2024 : International Conference on Autism
Conference Location : Montreal, Canada
Conference Dates : August 05-06, 2024