Symposium 6: Stem cell derived neurons for studying human neurological disorders (Thu July 29, 9-11AM JST)
Chairs: Jun Yao (Tsinghua University, China) and Jinju Han (KAIST, Korea)

9:00-9:30 Jinju Han (Grad Sch Med Sci & Eng, KAIST, Korea)
microRNAs in neuronal development and diseases

9:30-10:00 Yan Liu (Nanjing Medical University, China)
Suppressing the DSCAM/PAK1 pathway reverses neurogenesis deficits in Down Syndrome patient iPSC-derived cerebral organoids

10:00-10:30 Tomoyo Sawada (Lieber Inst. for Brain Development, Baltimore, USA)
Dissecting molecular bases of schizophrenia with iPSC-derived brain organoids and postmortem brain tissues

10:30-11:00 Jun Yao (Tsinghua University, Beijing, China)
Investigating the pathogenesis of bipolar disorder using combined iPSC and mouse models

Symposium 6 Speaker 1

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microRNAs in neuronal development and diseases

Neural stem cells (NSCs) are able to self-renew and differentiate into neurons. The balance between the two abilities of maintaining stemness and inducing differentiation of NSCs determines the efficiency of neurogenesis. Small non-coding RNAs regulate diverse cellular processes, including neuronal development, by mainly modulating gene expression at the posttranscriptional level. Specifically, microRNAs display dynamic expression profiles during neuronal differentiation, indicating the functional significance of microRNAs in neuogenesis. While a few microRNAs coordinating neurogenesis have been reported, the biological roles of most of the other microRNAs in neurogenesis are not completely understood. To identify microRNAs critical in regulating neurogenesis, we performed microRNA microarrays using RNAs from NSCs and differentiated neurons. From the list of microRNAs that change expression level during neuronal differentiation, we selected a NSC-enriched microRNA and a neuron-enriched microRNA, then investigated how they contribute to neurogenesis. We found the NSC-enriched microRNA and its primary target gene that controls migration of newborn neurons in the adult hippocampus. We further studied the association of the NSC-enriched microRNA to human brain diseases and found dysregulation of the microRNA in hippocampal NSCs generated from schizophrenic patient-derived induced pluripotent stem cells. This study shows the significance of posttranscriptional gene regulation in neuronal development and diseases. We are currently working on the neuron-specific microRNA to identify the biological roles of the microRNA and to unravel pivotal molecular mechanisms underlying neurogenesis.

Symposium 6 Speaker 2

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Suppressing the DSCAM/PAK1 pathway reverses neurogenesis deficits in Down Syndrome patient iPSC-derived cerebral organoids

Down syndrome (DS), caused by trisomy of chromosome 21, occurs in 1 of every 800 live births. Early defects in cortical development likely account for the cognitive impairments in DS, although the underlying molecular mechanism remains elusive. Here, we performed histological assays and unbiased single-cell RNA sequencing (scRNA-seq) analysis on cerebral organoids derived from four euploid cell lines and from induced pluripotent stem cells (iPSCs) from three individuals with trisomy 21 to explore cell type-specific abnormalities associated with DS during early brain development. We found that neurogenesis was significantly affected based on diminished proliferation and decreased expression of layer II and IV markers in cortical neurons in the subcortical regions; this may be responsible for the reduced size of the organoids. Furthermore, suppression of the DSCAM-PAK1 pathway which showed enhanced activities in DS) via CRISPR/Cas9, CRISPRi or small-molecule inhibitor treatment reverses abnormal neurogenesis, thereby increasing the size of organoids derived from DS iPSCs. Our study demonstrated that 3D cortical organoids developed in vitro are a valuable model of DS and provided a direct link between dysregulation of the DSCAM-PAK1 pathway and developmental brain defects in DS.

Symposium 6 Speaker 3:

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Dissecting molecular bases of schizophrenia with iPSC-derived brain organoids and postmortem brain tissues

Schizophrenia is a devastating neurodevelopmental/psychiatric disorder that affects ~1% of the population worldwide. Due to the complex genetic/environmental etiologies, sporadic occurrence and lack of many screenable intermediate phenotypes with a robust association to the disorder, the molecular underpinning of schizophrenia is poorly elucidated. Human pluripotent stem cells enable research on previously inaccessible human-disease-relevant cells. Recent genomic analysis and iPS cell-based modeling have identified several candidate cellular pathways in schizophrenia, including alterations in excitatory synaptic function. Genetic heterogeneity, however, has hampered to confirm the disease relevancy of those cellular phenotypes. Here, we will discuss our recently established organoid model of psychoses with a well-controlled genetic background with iPSCs from monozygotic twins discordant for the disorders. Single-cell RNA-seq of the organoids identified an accelerated maturation and enhanced GABAergic specification of the patient-derived neuronal cells suggesting that a developmental excitation-inhibition imbalance underlies the psychoses. We will also introduce our functional genomics approaches with iPSC-derived brain organoids, postmortem brain tissues of the patients and genome editing technique to dissect convergent cellular/molecular mechanisms of schizophrenia.

Symposium 6 Speaker 4:

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Investigating the pathogenesis of bipolar disorder using combined iPSC and mouse models

Bipolar disorder (BD) is a severe neuropsychiatric disorder that affects ~1-3% of the population worldwide. However, compared to other major mental illnesses such as schizophrenia and autism, the research progress for pathogenesis of BD has been lagging behind. This is largely because animal models based on susceptible genes or environmental stresses have often failed to show spontaneous cycling of mania and depression, the core symptom of BD. This supports a complex multigenic origin of BD. However, pedigree analysis has suggested a very strong heritability of BD symptoms, leading to a question regarding how the 'multigenic' deficiencies in the parent can be stably inherited by the majority of offspring. Using iPSC technology, we considered that regardless of the diverse genetic deficiencies carried by BD patients, at least a subgroup of BD patients likely share identical molecular deficits that lead to the mood symptoms. We combined animal and iPSC investigations, as well as clinical studies, and found that Synaptotagmin-7 (Syt7) is likely a key factor involved in the pathogenesis and inheritance of BD, and elucidated that Syt7 deficit-induced GluN2B-NMDAR dysfunction is a key mechanism for the induction of mania.