Accurate modeling of neurodevelopmental disorders using patients'-derived iPS cells

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Previous studies have suggested the abnormal central nervous development as the causes of psychiatric disorders, however, much remains unknown about the molecular and cellular etiology of these disorders. In addition to the potential cumulative effect of a large number of common genetic variants with small individual effects, psychiatric disorders are strongly associated with rare variants with high penetrance. Recent studies have suggested that *de novo* mutations, genomic spontaneous mutations identified in an affected child, but not unaffected parents, contribute to the risk of psychiatric disorders. Recently, we and other groups have identified that *POGZ* is one of the most recurrently *de novo* mutated genes in patients with autism spectrum disorders (ASD), suggesting that *de novo POGZ* mutations can be associated with ASD pathogenesis. Using iPSC technology, we have identified the role of POGZ in central nervous system development. In addition to *de novo* point mutations, we have been focusing on copy number variants, which represent large genomic duplications or deletions, and found that 3q29 deletion impaired central nervous system development in patient's-derived neural stem cells. These findings provide important insights into the cellular basis of ASD.

3-JPS-2 JPS Satellite Symposium

Reverse translational neuroscience research to unravel the causes of intractable diseases

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Recent technological innovations have led to the discovery of induced pluripotent stem (iPS) cells, and it has become possible to analyze the mechanisms of disease onset. In addition, DNA recombination systems such as the Cre/loxP system are used to specifically control target gene expression in the rodent brain. In the present study, by combining human disease-specific iPS cell research and *in vivo* neuroscience research, we tried to investigate the mechanism by which dopaminergic neurons are selectively affected in Parkinson's disease. In a study with human iPS cells, we found a significant increase in catechol-O-methyltransferase (COMT) expression in dopaminergic neurons along with epigenetic modifications including DNA hypomethylation. Furthermore, in an *in vivo* Cre/loxP-transgenic study, overexpression of COMT in dopaminergic neurons of the substantia nigra of mice induced cataleptic behaviors. These approaches are useful techniques for applying a patient's information to basic neuroscience research. In this symposium, we will outline and discuss the practice of "reverse translational neuroscience research".

Unveiling the impact of epigenetic regulation in disease pathogenesis with iPS cell technology

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Stepwise epigenetic reorganization occurs during reprogramming of somatic cells into induced pluripotent stem cells. The faithful shutdown of the somatic program occurs in the early stage of reprogramming. Taking advantage of such properties of cellular reprogramming, we examined the effect of *in vivo* reprogramming on *Kras*-induced cancer development. We show that the transient expression of reprogramming factors in pancreatic acinar cells results in the transient repression of acinar cell enhancers, which are similarly observed in pancreatitis. We next demonstrate that *Kras* and *p53* mutations are insufficient to induce ERK signaling in the pancreas. Notably, the transient expression of reprogramming factors in *Kras* mutant mice is sufficient to induce pancreatic ductal adenocarcinoma. In contrast, the forced expression of acinar cell-related transcription factors inhibits the pancreatitis-induced activation of ERK signaling and development of precancerous lesions in *Kras*-mutated acinar cells. These results underscore a crucial role of dedifferentiation-associated epigenetic regulations in the initiation of pancreatic cancers. We propose that iPS cell technology could be a powerful tool to study the impact of epigenetic regulation in disease pathogenesis.

3-JPS-4 JPS Satellite Symposium

Regenerative Medicine and Drug Development using Stem Cells

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There is an increasing interest in the induced pluripotent stem cells (iPSCs)-based regenerative medicine for various diseases. We have been developing regenerative medicine of spinal cord injury (SCI) by the transplantation of neural stem/progenitor cells (NS/PCs)-transplantation for many years. In a series of our previous efforts, we have addressed the issues of safety and tumorigenesis using iPSCs-derived NS/PCs (iPSCs-NS/PCs). The first-in-human clinical study of iPSC-based cell therapy for subacute SCI was approved by the government on February 18, 2019 as class I regenerative medicine protocol, which will be provided for under Japan's Act on the Safety of Regenerative Medicine.
I will also talk about our new clinical trial for ALS using a drug named ropinirole (ROPI: known as D2 receptor agonist), which was identified in the iPSCs-based phenotypic screening of ALS patients-derived motor neurons with FDA-approved drug library (Fujimori et al., Nat Med, 2018). Based on our findings on the potential anti-ALS action of ROPI, we started A Phase I/IIa, to verify the safety and tolerability of "ROPI" in subjects with ALS (ROPALS trial) from December, 2018. Notably, we will also generate iPSCs from patients and compare in vitro and in vivo effects of ROPI on ALS phenotypes.