Current Topics

Translational Research in Neurodevelopmental Disorders: Development of Etiology-Based Animal Models

Foreword

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Recent findings from genome-wide association studies (GWAS) have indicated a genetic overlap between schizophrenia and childhood-onset psychiatric disorders such as autism-spectrum disorders, intellectual disability, and attention-deficit hyperactivity disorder (AD/HD). A recent study has indicated that large, rare chromosomal deletions and duplications known as copy number variants (CNVs) identified in an AD/HD cohort were significantly enriched for loci previously reported in both autism and schizophrenia. Those studies suggest an overlap of genetic susceptibility and pathogenesis across the categories of schizophrenia, autism, and AD/HD.

Schizophrenia is a devastating psychiatric disorder that affects approximately 1% of the population with high heritability (80%). It is characterized by the presence of three major symptoms: positive symptoms (hallucinations, delusions, and psychosis); negative symptoms (anhedonia, social defects, and impaired motivation); and cognitive deficits (impaired working memory, attention, and execution). Schizophrenia is now regarded as one of the neurodevelopmental disorders. Accordingly, in the pathology of schizophrenia, disturbances caused by genetic susceptibility factors and environmental impacts during the neurodevelopmental period may impair brain maturation in the early neonatal stage, leading to the onset of disease mainly after puberty. Among genetic susceptibility factors for schizophrenia, some have a potential role in neurodevelopment. Maternal viral infection in the first and second trimesters of pregnancy is a well-known environmental factor increasing the risk of schizophrenia in offspring. The interaction between environmental and genetic susceptibility factors during neurodevelopment is proposed as a promising etiology of schizophrenia.

Childhood-onset psychiatric disorders, such as autism and AD/HD, affect many school-age children, leading to a lower quality of life, including difficulties in school and personal relationships which persist into adulthood. Autism is a neurodevelopmental disorder with a high heritability of approximately 90% and is characterized by core behavioral symptoms, including profound deficits in social interaction, re-

stricted interest, stereotyped responses, and other repetitive patterns of behavior. AD/HD, one of the most prevalent childhood psychiatric disorders, affects 5–8% of school-age children and is characterized by the core symptoms of hyperactivity, impulsivity, and impaired sustained attention. There are multiple genetic and environmental risk factors with small individual effects that may act in concert to create a neurobiological basis for childhood-onset psychiatric disorders. Multiple lines of evidence support the evidence of structural abnormalities such as reduced brain volume and thinner cortices, and cortical development is delayed by several years in children with AD/HD compared with typically developing children.

Various animal models have been developed that reflect genetic alterations in neurodevelopmental disorders. It is extremely challenging to model human neuropsychiatric disorders in rodents because of the subjective nature of many symptoms, and lack of biomarkers and objective diagnostic tests. It is also impossible to model an entire psychiatric disorder in a single mouse model. However, such animal models are extremely valuable in disclosing the specific role of a gene, signal pathway, or neuronal subtype in abnormal behaviors.

In this series of mini-reviews, the current state of animal models for neurodevelopmental disorders is reviewed with a focus on schizophrenia, autism, and AD/HD. Dr. Lu *et al.* introduce genetic mouse models for schizophrenia and discuss the neuropathological and behavioral abnormalities in each mouse model. Dr. Nagai and colleagues focus on a mouse model of schizophrenia which reflects gene-environment interactions. Dr. Higashida *et al.* focus on *Cd38* gene-knockout juvenile mice as an animal model of autism, in comparison with phenotypic changes in oxytocin gene-knockout mice and oxytocin receptor-gene knockout mice. Dr. Arime and coworkers introduce some animal models of AD/HD and discuss their advantages and limitations. I believe that these mini-review articles are useful and valuable for future studies on identifying the etiology of the disorders as well as potential new drug targets.