Drosophila Models of Complex Neurological Disorders in Humans

Young Ho Koh

Ilsong institute of life science, Hallym University

Anyang, Kyung-gi Do, Korea

My research program is utilizing the fruit fly *Drosophila* as a powerful biological system to address fundamental questions concerning complex neurological disorders in humans. Complex neurological disorders are common, sporadic forms of neurobehavioral diseases, including Alzheimer's disease, Amyotrophic lateral sclerosis, Dystonia, Epileptic Seizures, and Parkinson's diseases. Complex disorders are most likely to be caused by interaction of multiple genetic mutations or combinations of genetic and environmental risk factors. Predisposing genetic mutations may induce abnormal brain wirings, altered synaptic architectures and functions, imbalances in neurotransmitters, defective neuronal activities, or death of selected types of neurons that are increasing the person's susceptibilities to the onset and progress of complex disorders that are triggered by another genetic mutation or environmental risk factor. Because there is no cure, of utmost important is to identify genetic triggers and suppressors of complex disorders in order to prevent out-break of these disorders and to develop treatments ameliorating severe symptoms of affected individuals as well. Thus, identifying genes that modify behavioral symptoms and characterizing their functions in pathogenesis of complex disorders are the key goals.

In this seminar, I am going to discuss a *Drosophila* model of early onset torsion dystonia. Dystonia is the third most common movement disorder in humans and is characterized by involuntary muscle contractions resulting in severe twisting movements and abnormal postures. The most severe and common form is early-onset torsion dystonia, which is caused by a dominant mutation (a single amino acid deletion) in human TorsinA (ΔE HtorA) (Ozelius et al., 1997). Although this disorder

is transmitted in an autosomal dominant manner, only 30-40% of heterozygous individuals are afflicted indicating that DYT1 dystonia is one of many complex neurobehavioral disorder whose pathogenesis requires a predisposing mutation in combination with other genetic triggers and/or environmental risk factors for disease manifestation. I have established the first animal model for early-onset torsion dystonia by expressing ΔE HtorA in the nervous system of fruit fly *Drosophila*. I have found that ΔE HtorA flies exhibit severe locomotor abnormalities associated with structural defects at synapses. These phenotypes occur in parallel with the formation of ΔE HtorA protein aggregates that localize to synaptic membranes as well as nuclei and endosomes. Several lines of evidence suggested that ΔE HtorA could interfere with a signaling pathway between synaptic terminals and nuclei. Furthermore, overexpression of *Drosophila* or human Smad2, a downstream effector of the TGF-β signaling pathway suppresses the behavioral and morphological defects associated with ΔE HtorA expression. Therefore it is suggested that impaired TGF-β signaling underlies the defects observed in ΔE HtorA-expressing flies and may contribute to the human disease phenotype as well.

Now I am investigating molecular and cellular mechanisms underlying the production of protein aggregates or intracellular inclusion bodies in neurons, in order to provide essential information that will increaseour understanding in neurological disorders and provide new strategies for developing treatments of affected individuals. These studies discussed in this seminar could make significant contributions to (I) identifying at-risk groups both for disease onset and progress during the preclinical period by enhanced diagnosis, (II) accelerating the development of drugs that might modulate disease progression during the preclinical or clinical periods, (III) understanding molecular and cellular etiologies of complex neurological diseases in humans, (IV) providing new targets for pharmaco-genetic research aimed at ameliorating symptoms of afflicted individuals.