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Defining conserved spinal muscular atrophy gene networks that are involved in neuromuscular system using Drosophila SMA model

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Spinal Muscular Atrophy (SMA) is a devastating inherited disorder characterized by progressive loss of motor activity, failure of neuromuscular synapses and muscle weakness. Genetic cause of SMA is mutation of Survival Motor Neuron 1 (*SMN1*) gene, while genetic factor determining severity of symptom is copy number of Survival Motor Neuron 2 (*SMN2*) gene, which only generate small amount of SMN protein due to skipping a functionally important exon at high frequency. As SMN has been considered as a key factor to regulate neuronal cell function cell autonomously, up-regulating SMN protein in spinal cord motor neurons at pre-symptomatic stages is the most advanced therapeutic approaches to prevent, or, at least, delay irreversible loss of motor neurons. However, the fact that SMA patients exhibit muscle weakness and experience fatigue suggests that it is little known underlying mechanism how low SMN levels affect to trans-synaptic biology at the neuromuscular junction (NMJ). Trans-synaptic structure and signaling at the NMJ play important roles for establishment and maintenance of neuromuscular connectivity and functions. As pathological observation in post-mortal NMJ specimen or rodent SMA models exhibited abnormality in neuromuscular connectivity, utilizing Drosophila NMJ, which is well characterize its structure and molecular mechanism, allow us to understand how low levels of SMN perturbs structure and molecular mechanism at the NMJ in depth. Severe SMN mutants exhibited two phenotypes in motor unit known as SMA pathology, loss of motor axon and abnormality at the NMJ. Modulation of trans-synaptic two canonical signaling pathways, BMP and FGF signaling, that have shown genetic interaction to SMN, can rescue the SMN defects. In addition, each pathway seems to modulate distinct aspect of SMA motor unit pathology.

Biography

Takakazu Yokokura has his expertise in genetics and molecular biology and passion in finding approaches to cure devastated neurological disorders, such as Spinal Muscular Atrophy (SMA) and amyotrophic lateral sclerosis. His study has focused on elucidate underlying molecular mechanisms that low levels of SMN leads to manifestation of SMA neuromuscular pathological phenotypes.

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