論文内容の要旨

論文題目：Molecular mechanisms of interaction between a neuron and its target cell during synaptogenesis

（シナプス形成過程における神経―標的間相互作用の分子機構）

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As an initial step to comprehend the function of a complex nervous system, I took a reductionistic approach and examined the development of synapses, the sites of cell-cell communication, at the molecular and cellular levels. Although synapses are considered to emerge through interaction between a synaptic pair, reports on retrograde signaling transmitted from post- to presynaptic cell *in vivo* are relatively scarce. I have thus examined the active role of target cells during synapse formation at *Drosophila* neuromuscular junction. Specifically, by using fly genetics, I have manipulated the calcium/calmodulin-dependent protein kinase II (CaMKII) signaling pathway within the postsynaptic cells and examined its effect on synapse formation. Electrophysiological recording showed that synaptic transmission was strengthened by postsynaptic activation of CaMKII. Morphological analyses demonstrated that increase in the presynaptic area and the number of neurotransmitter release sites were the underlying mechanisms of functional enhancement. Since the modulation occurred across the synaptic cleft, it suggested the existence of retrograde signaling. I have further revealed that the

major constituents of synapses, namely a cell adhesion molecule Fasciclin II and a scaffolding protein Discs Large, are necessary for the signaling. These results provide a novel view that pivotal synaptic constituents must be coordinately regulated to transfer retrograde messages.

Besides, I have examined the dynamics of Ca^{2+}, a prime second messenger and the activator of CaMKII, within the postsynaptic muscle cell during synaptogenesis. In the course of Ca^{2+} imaging, I have found spontaneous and transient rises of green autofluorescence in muscles. The fluorescence originated in flavoproteins, and was dependent on the presence of extracellular Ca^{2+}. Since the fluorescent signals were stronger near synaptic sites and their rate of emergence was influenced by neuronal innervation, they may be related to the development of synapses. Considering the fact that flavoprotein fluorescence is correlated with intracellular Ca^{2+} concentration, the autofluorescence imaging may serve as a new non-invasive method to investigate the role of postsynaptic Ca^{2+} in synaptogenesis. Together, this dissertation addresses the active functions of target cells during synapse formation.