

INVITED LECTURE T3

Signal Transduction and Propagation in Synapse Formation

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In response to motor innervation, acetylcholine receptors (AChRs) are redistributed into high-density (10,000 per μm^2) clusters at the postsynaptic membrane of vertebrate neuromuscular junction (NMJ). This remarkable molecular and structural specialization of the plasma membrane is accomplished by a muscle-intrinsic mechanism in conjunction with signals from the innervating motor axon. Studies over the past decade have suggested the following paradigm in understanding the NMJ formation: motor axons secrete the heparan-sulfate proteoglycan termed “agrin” to cause the local activation of a tyrosine kinase receptor called “MuSK” (muscle-specific kinase) to initiate a signaling cascade leading to the assembly of a postsynaptic cytoskeletal scaffold that clusters AChRs through a diffusion-mediated process. With quantum-dot nanoparticles, we have recently obtained direct evidence on the diffusion-trap process in AChR clustering. In addition to the kinase pathway, we found that tyrosine phosphatase (PTP) is also activated as a result of synaptogenic stimulation of muscle. PTP signal locally checks the spread of the kinase signal in effecting a sharp boundary of AChR clustering. In addition, it also globally suppresses the formation and maintenance of AChR clusters in the extrajunctional area. This indicates that PTP serves as a negative regulator in postsynaptic development and its influence is both local and global. Our recent work has shown that MuSK, Src family kinase, and the SH2 domain-containing PTP Shp2, together with its activating protein, are integral components of the mechanism for the propagation of the PTP signal. Thus, a locally activated kinase signal coupled with a diffuse and propagating PTP inactivator enables the muscle to form a spatially discrete and preeminent postsynaptic specialization for highly efficacious neurotransmission.

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