Local and Global Signaling in Neuromuscular Synaptogenesis

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At the vertebrate neuromuscular junction (NMJ), signal transmission from the nerve to the muscle in causing muscle contraction is mediated by highly efficient release of acetylcholine from the nerve terminal and the sensing of this molecule by acetylcholine receptors (AChRs) in the muscle. This is accomplished by the clustering of AChRs in the postsynaptic membrane opposite to the nerve terminal and the focal accumulation of ACh-containing synaptic vesicles in the nerve terminal. In this presentation, the cellular and molecular mechanisms that govern the development of the postsynaptic membrane will be discussed. Recent studies have established the central role of motoneuron-derived heparan-sulfate proteoglycan (HSPG) agrin as an inducer for NMJ development. Agrin activates the receptor tyrosine kinase MuSK to effect AChR clustering, but this reaction requires a yet unidentified cofactor since agrin does not by itself bind to MuSK. Our study has implicated the role of HSPG-bound growth factors as partners in agrin's action. Once activated, the kinase cascade leads to local actin polymerization which serves as a scaffold for organizing the postsynaptic apparatus. In addition to tyrosine kinases, postsynaptic induction also leads to tyrosine phosphatase activation which helps define the boundary of synaptic AChR clustering and effects dispersal of extrajunctional clusters. These signaling events are facilitated by the intimate pericellular interaction between the synaptic partners facilitated by myopodia, muscle-derived filopodia-like processes. They are generated as a result of agrin stimulation and mediate the formation of adherence junctions between the nerve and muscle. Our findings thus illustrate the interplay between nerve-derived and muscle-intrinsic factors in the assembly and sculpturing of the synaptic specializations.

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Host: **A/P Sheu Fwu-Shan**

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Seminar Announcement

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