Formation and Function of the Neuromuscular Junction

People are judged by their actions, and these actions are coordinated by nerve cells and carried out by muscle cells. So an understanding of nerve and muscle is fundamental to our knowledge of how the human body functions.

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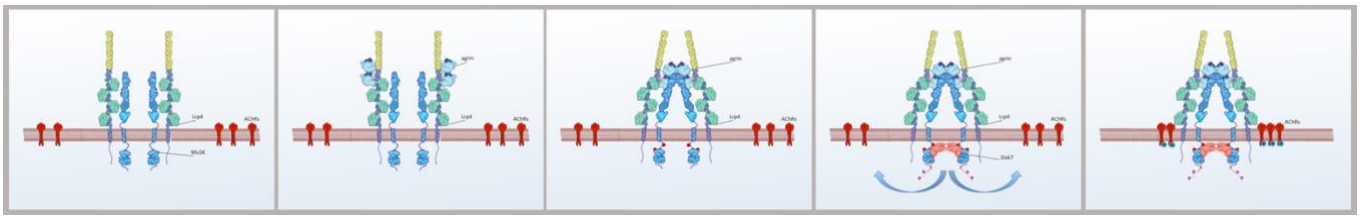
Synapses are essential relay stations that confer information between cells. Synapses form between neurons or as in the case of the neuromuscular synapses between a motor neuron and a muscle fiber. The neuromuscular synapse, also known as neuromuscular junction, regulates every movement within our bodies including breathing and therefore is critical for survival. In addition, the neuromuscular junction has been a popular model system for synapse formation due to its size, simplicity and accessibility. Much of the information about neurotransmitter receptor function and assembly at synaptic sites comes from studies on the neuromuscular junction.
A neuromuscular junction forms when a motor axon reaches a muscle fiber. Signals from the nerve induce differentiation of the postsynaptic muscle membrane and in turn, signals from the muscle induce differentiation of the presynaptic nerve terminal. A hallmark of postsynaptic differentiation is the concentration of acetylcholine receptors (AChRs), the receptors for the neurotransmitter acetylcholine, at synaptic sites. AChRs are present at a concentration of >10,000 molecules per μm^2 at synapses compared to <10 molecules per μm^2 in the extra-synaptic membrane. This high concentration of AChRs ensures a reliable and stable transmission of action potentials to the muscle necessary to govern all movements within the lifetime of a vertebrate organism.



MuSK signaling at the neuromuscular synapse

Agrin, an extracellular heparan proteoglycan produced by motor neurons, the Low-Density-Lipoprotein-Receptor-related Protein 4 (Lrp4) and MuSK, a muscle-specific kinase, are the key players in neuromuscular junction formation. The critical events during synapse formation include Agrin-Lrp4-mediated activation of MuSK, concentration of MuSK at the synapse and tyrosine phosphorylation. Signal transduction downstream of MuSK regulates AChR clustering but the exact mechanism of action is unclear.
In ongoing studies, we use molecular and biochemical approaches to characterize events downstream of MuSK and their role in AChR clustering.

Characterization of mutations that cause congenital myasthenic syndromes

Failure of neuromuscular transmission occurs in a large array of rare life-threatening diseases. Among them, the congenital myasthenic syndromes (CMS) constitute a rare group of heterogeneous genetic disorders caused by mutations in genes encoding various proteins involved in neuromuscular transmission or in more general processes such as glycosylation. There is no cure for CMS, and life-long medications are mainly symptomatic and often show deleterious side effects.
We study MuSK and Agrin mutations identified in CMS patients using functional in vitro assays and cell models to elucidate at the molecular level how these specific mutations affect neurotransmission as well as NMJ development and function.

Recent Publications

Rodríguez Cruz PM, Cossins J, Cheung J, Maxwell S, Jayawant S, Herbst R, Waithe D, Kornev A, Palace J, Beeson D. Congenital myasthenic syndrome due to mutations in MUSK demonstrate that control of the level of MuSK phosphorylation is crucial for governing synaptic structure. Hum Mutat. 2019 Nov 25. doi: 10.1002/humu.23949.

Herbst R. (2020), MuSk function during health and disease. Neurosci Lett. 2020 Jan 18;716:134676. doi: 10.1016/j.neulet.2019.134676.

Gemza A, Barresi C, Proemer J, Hatami J, Lazaridis M, Herbst R. Internalization of Muscle-Specific Kinase Is Increased by Agrin and Independent of Kinase-Activity, Lrp4 and Dynamin. Front Mol Neurosci. 2022 Mar 15;15:780659. doi: 10.3389/fnmol.2022.780659.

Prömer J, Barresi C, Herbst R. (2023) From phosphorylation to phenotype - Recent key findings on kinase regulation, downstream signaling and disease surrounding the receptor tyrosine kinase MuSK. Cell Signal. 2023 Apr;104:110584. doi: 10.1016/j.cellsig.2022.110584