New mechanisms regulating acetylcholine receptors at the neuromuscular junctions

Neuromuscular synapses (NMJs) are specialized junctions between motor neurons and fibers of skeletal muscles. Their role is to transmit neuronal impulses, which elicit muscle contraction in coordinated limb movements and respiration. NMJ comprise also Schwann cells, which play an important role, coordinating the formation and functioning of other synaptic components. NMJs, like synapses in the brain, also undergo the process of synaptic plasticity during development and in response to injury. In the early postnatal life, NMJs are small and have a simple plaque-like appearance. With time these structures become perforated with scattered openings and eventually form a complex pattern resembling a pretzel. The significance of this elaborate NMJ architecture is not fully understood but is postulated to affect the fidelity of synaptic transmission and coordination of muscle contraction. Furthermore, abnormalities in NMJ developmental remodeling are frequently observed in various disorders of the neuromuscular system. Nearly 300 such pathologies (often lethal) have been identified, but the etiology of many of them remains unknown.

Major component of the NMJ postsynaptic machinery are receptors for the neurotransmitter (AChR). Despite decades of studies on them, we still know little about the mechanisms that regulate their cellular trafficking and stability at the postsynaptic membrane. We will try to understand the molecular mechanisms underlying these processes by identifying novel proteins that are recruited to the cytoplasmic domain of AChR. Additionally, we will study cellular localization and trafficking of a mutant of AChR, which is associated in humans with AChR insufficiency at the NMJs. It is currently unknown what the mutation does to receptors and how it affects its functioning. We will investigate the possibility that the mutation affects the recruitment of specific interacting proteins and, thus, influences AChR organization.